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CLINICAL AND EXPERIMENTAL

THE MEDICINE OF THE AMERICAN INDIAN*

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AS PRACTITIONERS of medicine we are in this day perhaps too prone to forget the value to medicine of the work of those who have preceded us, perhaps too much persuaded that modern medicine and modern science are only of value. We forget too easily that medicine like most other things is a matter of evolution and that most of our knowledge has in fact been based on a foundation of the experience and study of ages. I wonder sometimes whether we appreciate fully how absolutely dependent we are in medicine on what has gone before. How many of us are competent to practice medicine even today on the frontier away from the manufacturing pharmacist, away from our colleagues, from our journals, and from the basic facts in particular which have evolved from the studies of centuries past.

My observation has been that the modern scientifically trained student is in large degree more and more dependent on the facts and experiences which others have gleaned. Many, if not most of our research workers must base their investigations on a foundation of evolved knowledge which we take altogether too casually and with too little respect for its origin.

How many of us are competent to even set a fracture or to treat a serious wound away from the detailed assistance of the hospital and the carefully worked out preparations which we owe to others. Briefly how many of us with all our present knowledge might successfully practice the art of physic

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in the stone age, entirely without the assistance which others render to us? If one but thinks of this, better if one tries to meet the emergencies of practice away from drug stores, away from hospitals, without the microscope, and without the x-ray, how would we get on?

Hence it seems to me that it is well for us to study medical evolution, to interest ourselves in the pregnant subject of medical history, to learn of, as we shall certainly come to respect our predecessors in the practice of medicine and surgery. To do this one must acquire more than a passing knowledge of archeology and ethnology; one must delve sincerely into the customs and requirements of ancient peoples. Such a study is certain to broaden our knowledge and certain also to create in us a great respect for those men and peoples who with little inherited knowledge and no literature have none the less laid the foundations of medical art and science.

How many of us appreciate what we owe to those who gave us mercury, iodides, the salycylates, digitalis, the saline laxatives, cascara and aloes, quinine, cocain, alcohol, and the sedatives of the opium group? These and many other drugs on which we daily depend were discovered and properly used by the red man. Thousands of years before Witherington was born, the Indian of the southwest used infusions of Foxglove in heart disease, and if history is to be relied upon, he used it properly.

Another point which we must always bear in mind in these studies is that modern medicine as we term it could not as it now stands have been adapted to the needs of ancient man, chiefly because modern medicine is now dependent absolutely on the assistance of the chemist, the physicist, the bacteriologist, the pharmacist, and the manufacturer. The medicine of the stone age was necessarily also of the stone age; the electric knife was not available but the keen edged flake of obsidian was, and for that surgeon who is high-minded of his present-day skill, permit me to recommend that he try in his work only such tools as the stone age supplied, and then compare his results and skill with those of the surgeon of that day. If we will properly appreciate the medicine of primitive man, we must know his needs and the facilities furnished him; they were indeed very different from those of this day.

Perhaps as a class we less appreciate the history and the archeology of our native Americans than those of any other people. All of us know of ancient Egypt, of Rome, of Greece; we are, as properly educated men, tolerably familiar with those ancient peoples, and we know a good deal of their medicine and of the basic knowledge which they evolved on which modern medicine depends absolutely and hourly. How many of us realize the fact that here in America we had a civilization which exceeded and preceded in art, mathematics, astronomy, architecture, agriculture, politics, and which certainly equalled even in theology that of any of the ancient peoples of Europe.

In Bolivia still stands, in spite of Spanish cupidity and religious intolerance, the devastated fragments of a city, greater in its architecture and in its sculpture than anything that Greece or Italy ever produced, and it preceded

the culture of these countries by at least several thousand years. How many of us realize that when the Spaniard came to America he found a civilization in certain areas which exceeded his own of that very time except in the two particulars of military organization and in navigation. For those of you who are skeptics, may I recommend that you read Mason's "Columbus Came Late," or still better for the more serious minded and studious of you, read Verrill's "Old Civilizations of the New World." For those of you who still doubt, instead of going on your next vacation to Greece or Egypt, go to Tia-huanaco in Bolivia, to Cusco, to Yucatan, Guatamala, or Honduras. Study in the museums of Lima or in the easily accessible and marvelous collections of the City of Mexico, or if still in doubt precede your own explorations by a visit to the Museum of the American Indian, Heye Foundation here in your own city. Many beautiful and marvelous things of ancient American origin are also to be seen any day in the American Museum of Natural History, any one of which must convince you that here in our own America we possessed a civilization and an art more marvelous than anything of its kind in Africa or Europe.

With this introduction permit me then to talk with you for a few moments concerning the medicine of the American Indian. At the outset it is important for you to understand that under the heading of the American Indian, a tremendous field is included. To conceive of the American Indian as a single race or people is as absurd as to speak of the Europeans as a single class group. The American Indian varies as widely in his tribal civilization standards and types as does the Italian from the Icelander. What I have to say to you this evening is chiefly of certain of the tribes with which I have been most familiar, of the Ojibways, the Sioux, the Blackfeet, the Apache, the Navaho, and something of the Pueblo people. I thus limit myself because I know so very much less of the medicine of the South American Indian including the tribes of Mexico, Honduras, Guatamala, Chili, Peru, Bolivia, of the Myas, the Guiamacs, even of the Astecs and Preastecs; and yet we know that these tribes exceeded in civilization, art, agriculture, architecture, sculpture, and astronomy the tribes of which I am to speak mostly tonight as much as the modern Englishman or German exceeds the Laplander or Esquimo of today. Of these tribes have sprung such heroes, statesmen as Tecumseh, as Bolevar, Pofiero Diaz, Cailles, Rubio, and others who are truly world figures and not merely citizens of one land or one people. Occasionally, as in comparison, I shall refer to the medicine of the southern Indian, drawing for my knowledge on the little that I have seen and from what I have read.

Also in passing I should like to say that inevitably the white man has lowered and befouled the Indian of whatever tribe by his religion and by his military methods. In these characteristics only, it seems to me, have we outdone the Indian; these have been the two channels through which we have "civilized" the red man.

Before it is possible to go on, may I tell you something of what the red man, whose medicine I am to speak to you of this evening, was. Perhaps I

can do no better than to quote at the outset what Colden says of the Iroquois, our predecessors in New York.*

On the death of Lieut. Governor de Lancy in 1760, Colden came to New York as Governor; he was appointed Lieut. Governor in 1761. He produced a great mass of geographical, metaphysical, medical, and theological learning and literature. He was the son of a Scotch clergyman and was designed for the clergy, but he took up finally the study of medicine. He practiced after his graduation in England, for some time in Pennsylvania, and later, because of his distinction, he became surveyor general of the colony in New York. He was made a master in Chancery and received a large grant of land near the town of Montgomery in Orange County. He was regarded in England as the best informed man in the New World on the affairs of the British colonies in America. He was an early observer of the influence of climate on health. He was just and fair to the Indians, was much honored by them and was adopted by the Mohawks of Canajoharie. The books cited were apparently written to inform Great Britain on the Indian question and to stress the strength and importance of the Iroquois Federation with which he was keenly informed and sympathetic. He died at Spring Hill, near Flushing, on the twenty-first of September, 1776. His many manuscripts are safe in the archives of the New York Historical Society but little is commonly known of him now though he was for his times one of the most learned in electricity, in natural philosophy, and in history. He was the valued associate of Franklin, a correspondent of Linnaeus, Grovinus and with other eminent authorities in the natural sciences. He was always keenly alive to the scientific medicine of the day though his important executive obligations required his giving up medical practice.

He says: "The Five Nations are a poor and generally called barbarous people, bred under the darkest ignorance; and yet a bright and noble genius shines through these black clouds." "None of the greatest Roman Heroes have discovered a greater love to their country or a greater Contempt of Death than these People called Barbarians have done, when Liberty came in Competition. Indeed I think that our Indians have outdone the Romans in this Particular; some of the greatest of those have we know murdered themselves to avoid Shame or Torments; but our Indians have refused to die meanly, or with but little pain when they thought their country's Honor would be at stake by it; but have given their bodies willingly to the most cruel of torments of their Enemies, to showe as they said, that the Five Nations consisted of Men, whoose Courage and Resolution could not be shaken."

"Instead of virtues we have only taught them Vices, that they were entirely free from befor[e] that time." "If care were taken to implant and cultivate in them that general benevolence to Mankind, which is the first true principle of Virtue—They would no longer deserve the Name of Barbarians, but would become a people, whoose Friendship might add Honor to the British Nation." "Their great Men, both Sachems and Captains, are gener-

*The History of the Five Indian Nations of Canada which are dependent on the Province of New York, and are barrier between the English and the French in that part of the World. By Hon. Cadwallader Colden. New Amsterdam Book Company, New York, 1902.

ally poorer than the common People; for they effect to give away and distribute all Presents or Plunder they get in their Treties or in War, so as to leave nothing to themselves."

The only writings which I have been able to secure of Governor Colden are concerning the history of the Indian wars and of their treaties. I have obtained nothing dealing with Indian Medicine. It is to be much regretted that a person of his medical training and scientific thought should not have written of the medical customs of these our predecessors in the medical practice of New York. It is very evident that he thoroughly respected and even admired these men. As to their political sagacity, trustworthiness and valor, he leaves little unsaid and where he recounts their cruelty and brutality, he is wont to compare it without honor to the white man with his religious persecutions and his retaliatory wars.

Clark Wissler of the American Museum of Natural History, one of our greatest living authorities on archeology and ethnology says (The American Indian): that the Indian stands out in his culture in sharp contrast to that of the old world, and that while we have replaced him in this land, we have absorbed a great deal of his culture, and that we have wrought great havoc by his withdrawal from painting, sculpture, and the decorative arts. This loss, though considerable would be small comparable to that if we were to lose from our economic life maise, cocoa, quinine, tobacco, potatoes, beans, squash, melons, and tomatoes, and what has evolved from our adaptation of their agricultural methods in the world. Irrigation, at least in this country is founded on Indian methods and procedures and their agricultural methods from the use of irrigation are still of immeasurable value to us today. I have seen beautiful irrigation systems installed by the prehistoric Indian, still in use today in Arizona, monumental systems which existed long before the advent of the white man. Wissler further says: "Imagine what would be lost to us if we could strike from our history, geography and literature all that pertains to the Indian!" The white man in many localities added but little beside iron and a more schooled and ruthless method of warfare.

Even our language, here in the new world has been in very large part taken from that of our red predecessors: we "hit the trail," we "pass over the divide," the camp fire, and the lodge circle have become endeared terms of our idiom, and a large number of us, in spite of our religious teachings still yearn to reach the "Happy hunting grounds." Our geographic names are in greater part adapted from those of the red man, our great railway systems, even our modern automobile highways for the greater part still follow the moccasin beaten pathways of the Indian, and most of our mannerisms and idioms which are typically American, evidence the survival in our culture, that of the red man. Colloquialisms and dramatic figures of American slang, poetry, and literature still portray the persistence and dramatic quality of the Indian orators, heroes, and statesmen.

In government, and particularly in the more idealistic forms expressed in altruistic communism, the world has never equalled the systems of the Pueblo peoples or that probably in vogue among the Mayas, Astecs, and

Toltecs. The League of the Five Nations in our own state of New York still represents a high water mark of organization and mutual consideration in governmental affairs. It was truly a league of nations, with ability, altruism, truth, and honesty in act as in theory.

I have already mentioned the deep impress which the Indian has made on our language. Notwithstanding the fact that the Indian peoples in the Americas have differed tremendously in traits, characteristics, in culture and in customs, as widely certainly as now exists between any of the civilized peoples of the whole world, still they possessed and still do, a mutual method of communication in the sign language which was almost universally understood and employed. It has interested me tremendously to note the strong similarity between this sign language of the Indians and that which our deaf and dumb now use. An Indian skilled in sign language, I am convinced would have little difficulty in understanding much or most of the sign language employed by the deaf and dumb, and the art of pantomime has never been more fully and beautifully demonstrated than by the orators of our primitive people.

In art, we have rarely as yet equalled that of the Indian, particularly in textiles exemplified by the beautiful and useful weaving of the South American tribes and the exquisite, when uncontaminated by white design, work of our Navahoes and Pueblos. We can never hope to equal the Indian in basketry, especially the work of the Pimas, Apache, and Supai, and the work of the ancient basket maker was never equalled, by even these artisans. In ceramics we can justly compare Indian antique work with that of the Chinese, for they have far excelled the Greeks in this work as well as in sculpture.

It is entirely inconceivable that such a people should not have had and practiced a system of medicine and surgery, comparable with their culture in other fields. The more we come to study their methods, the more do we become impressed with their skill and learning in these directions, especially in the field of traumatic surgery with which, naturally from the requirements of their habits of life, warfare and culture, they came most frequently in need.

Though I have been a student of Indian medicine since my early boyhood I know but little of the subject, but that little has created in me a feeling of great respect and admiration. Pioneer medicine in this country has been almost entirely derived from Indian methods, and I think that before I am done this evening I shall cause most of you to feel but honor and respect for the medicine of the American Indian. There are few methods of modern medicine which were not represented in kind, if not in precise technic by Indian methods, and we owe entirely to our Indian predecessors in the profession many of our most potent methods and drugs. Cesarean section, symphisiotomy, and the Credé method of placental expulsion, Verrill states (private communication) were practiced among certain of the more highly cultured tribes as those of certain districts in South and Southern America, long before Caesar was born. The same authority, corroborated by Hrdlicka and many other students of the subject, calls attention to the frequency and success of trephining of the skull and the use of artificial limbs ages before

the white man or even the Egyptians had advanced beyond the most primitive methods of medical or surgical procedure.

It is a curious and very unfortunate fact that the voluminous literature concerning Indian medicine and surgery has so very little to say concerning the practices of our most advanced and intelligent tribes, notably those of South America, of Central America and Mexico, where we know the highest types of civilization flourished, then present in the entire world. There are several reasons for this unfortunate state. Among these are the fact that most of the studies of these most advanced tribes have been made by ethnologists and archeologists who have had but little medical interest or schooling. Until we have discovered a Rosetta Stone which will unlock the secrets of the abundant records and codices of these peoples which we possess, we can expect to know only that of the medical and surgical practices of these people which has been handed down to the present descendants of these people. Yet we know that these tribes employed anesthetics for surgical procedures, notably cocain, peyote and other drugs while the white man was a barbarian who put his wounded in war to death by "mercifully slitting the wezand."

Concerning the medical methods of our northern tribes we have much more exact knowledge from the methods of pioneer medicine which have been handed down to us and very largely also because many of the early missionaries, who were themselves more or less medically trained have recorded their observations as in the records of the Jesuit fathers. Also in very large part because the medical officers of our little army have from the very first been interested in the subject and have recorded their studies and observations in official reports. Furthermore we must accord great credit to our ethnologists and archeologists in North America who have seriously interested themselves constantly in these important matters. Men such as Hrdlicka, Wissler, Verrill, Lieutenant Bourke, Colonel Dodge and even Lewis and Clark in their journals have given a hearing to this important field of archeology which has made it possible for us of the profession to derive, concerning our more northern tribes an understanding of the matter which has been and still is of great value and considerable accuracy. May I also give some credit to the numerous amateur archeologists of our profession who have given time and study to the subject.

Considerable information must be also attributed to the most bitter enemies of Indian Medicine from the days of Cortez to the present time, the theologians who have with few exceptions mentioned but to condemn, such writers as the malodorous Cotton Mather for example. The father of this person, the Reverend Mr. Increase Mather also wrote extensively in like vein. Mathers *Magnalia,* Book III, as Halkett quaintly says, solves the Gordian knot of the matter of the origin of the American Indian most satisfactorily perhaps from the standpoint of a theologian. This reverend authority says: "The natives of the country had been forlorn and wretched heathen ever since their first herding here; and though we know not when or how the Indians first became inhabitants of this mighty continent, yet we may guess that probably the devil decoyed those miserable salvages hither, in hopes that the

gospel would never come here to destroy or disturb his absolute empire over them." The amiable Increase cites as illustrative of this archeologic gem, the statement of an Indian about to be executed for a murder committed while he was drunk, who stated that the "missionaries minded their bottle more than their Bible."

John Halkett, Esq., author of "*Historical Notes, Respecting the Indians of North America, with remarks on the attempts made to convert and civilize them*" (London, 1825), stresses the point that a natural approach to the affections of the Indians would be through the introduction of medical men instead of clergymen. This author points out the greater success of the Jesuits with the Indians because most of this sect were more or less medically trained, and they found the Indians very receptive to such teaching and quick to adopt better methods of medical treatment. The powerful influence wielded by men of the high character and attainments of La Salle and Hennepin, men whose lives and examples tallied with their preaching was thus fully explained, and very much of our most accurate and truthful statements in regard to the social and medical life of the Indians of North America will be found in the pages of the Jesuit Relations.

Franklin's essay on "The North American Savages" also gives us a very honest and faithful account of them. He says: "Savages we call them because their manners differ from ours, which we think the perfection of civility; they think the same of theirs." Unfortunately with the advent of the white man, smallpox, gonorrhea, scarlet fever, measles, tuberculosis, and other epidemic infections appeared for the first time among the Indians, who quite correctly attributed these scourges to the advent of the white missionaries and traders. Hence, it is that the universal antagonism of missionaries to the medicine men naturally developed, especially since the medicine men in all tribes have exerted a powerful influence over their people not only in matters of disease and medical practice, but also in general social and political life, in their theology; and in most tribes the medical men have been also leaders in war; in many instances either associate or chiefs during all times of hostilities. Many of our most famous Indians were of this class, Tecumseh, Sitting Bull, Chief Joseph, Geronomo, and many others.

In most tribes, especially with those of higher types of civilization, the medicine men were selected from the more outstanding, pious, and studious men of the tribe, sometimes, however, because they had passed through some remarkable experience or training. In other tribes, as among us, any person might assert his abilities and if he was able to develop a following he was allowed to do so, but in most instances the aspirant for medicine man was required to pass through a long and severe course of study or training under the auspices of some older and credited preceptor. In certain tribes the office was hereditary and young boys were put under strict training almost from their birth. In a good many instances likely boys were selected by the medical clan and trained by the older and more experienced men for their important office.

In most instances theology has been combined with the practice of medicine and the medicine men have attended or supervised the religious and sac-

ramental ceremonies as well as being charged with the care of the sick and injured. In some of the more highly evolved tribes the priestly and medical functions were, however, entirely disassociated. In almost all instances specialties were practiced; men especially skilled in the treatment of the sick were differentiated from those who attended to surgical disease, for example. In most tribes obstetric practice was usually limited to women, and many of the better tribes recognized both men and women as medical practitioners, in which case consultations and combined practice was usually in vogue. Women, however, rarely took part in war councils or in actual warfare while the medicine men almost without exception did, and as a general rule they were expected to act with particular valiancy and courage, because of their standing in the political, intellectual and governmental phases of tribal life.

My chief experiences with Indian practitioners as it happens, has been with the Ojibway people. For five consecutive years it was my happy privilege to spend a time each fall with the son of one of the most distinguished medicine women of this fine tribe, and through this relationship I was able to come into rather more intimate contact with the people than would otherwise have been the case. This tribe had, and to some extent still has, a most complete organization of its medicine men and women, for in this advanced people, women, properly trained and accredited were also admitted to the medicine clan, the Midi or Midiwin. Happily also the medical clan of this tribe has been most carefully studied by competent ethnologists and probably the medical organization of this tribe has been more completely studied and detailed than that of any other tribe in existence. (Read book of Diamond Jeness.) Two women of this tribe and clan, Mary Bear and Mrs. Steve L'Africaine, wife of a local Hudsons Bay Company chief factor, became quite friendly with me, and through them I met other members of the Mediwin Society. The deep respect in which I came to hold these people has inevitably tinctured my attitude toward the Indian medicine man, a feeling but intensified by my less extensive experience with other tribes.

I shall attempt to give a garbled and very much abbreviated account of the organization of this society, largely gathered from reports and studies published by the American Bureau of Ethnology concerning the organization of the Midiwin.

The tenets of this society still permeate the Ojibway tribes and much of their medical practices are still derived from the society which is inextricably intertwined with the religion of this tribe.

Concerning these practices La Hontan (*New Voyages to North America,* London, 1703) says: "When they are sick they drink only broth, and eat sparingly and if they have the good luck to fall asleep, they think themselves cured. They assert that sleeping and sweating will cure the most stubborn diseases in the world. When they are ill they are visited by a sort of quacks, Jongleurs." Hennepin, in *A Continuation of the New Discovery,* speaks of these medicine men in a very resentful and critical manner. Marquette on the contrary, after referring to the Indian Herbs list and in mention of the calumet dance says: "They have Physicians among them, toward whom they are very

liberal when they are sick, thinking that the Operation of the Remedies they take is proportionate to the presents they make unto those who have prescribed them."

The symbol of the Fourth Degree of the Midiwin is the cross, and when Father Marquette found this he considered it as a compliment either to him or to his religion whereas is was but the symbol of one of the degrees of the Midiwin. In addition to the Midiwin these same Algonquin tribes have two other classes of priests or dealers in mystery, the Jessakkid and the Wabeno. These may or may not be members of the medical society, but their functions are quite distinct from those of the real practitioners who were members of the Midiwin almost without exception, except for certain general practitioners, as we would say of domestic or household medicine.

The Jessakkid is rated as a seer and prophet; the Wabeno is prompted by dreams and visions; he is a magician, indulges in exorcisms, etc. He may perhaps be rated in comparison to the regular practitioner of the Midiwin as the psychoanalyst is to us. The Jessakkid brings on evils and spells.

The existence of the society of the Midi is first cited by the Jesuit Relations about 1642. Probably the most understanding account of it, though confessedly very incomplete was published by an educated Ojibway, a member of the legislature of Minnesota, who also wrote the *History of the Ojibway Nation.* Warren states that even with his membership in the tribe, his perfect command of the language and his well recognized friendliness to his people, he was unable to secure absolutely authentic information as to the society, though Schoolcraft claimed to have been admitted as a member; if so he was probably the only white man who ever gained admission to the lodge; and Schoolcraft is quite generally thought to have been, to put it mildly, more picturesque than accurate in his statements.

Warren stated that the traditions and ceremonies of the society were not only transmitted by word of mouth but also by hieroglyphics and charts of ceremonies and procedures. These have of course now been largely lost or contaminated by admixture with the teachings of the missionaries of various sorts, by inattention and the lack of respect paid to the old men and their teachings by the younger generations.

The Rev. Peter Jones who was an educated Ojibway, serving as an Episcopal missionary, in his book (*History of the Ojibway Indians,* London, 1843) states that "each tribe has its medicine men and women, an order of priesthood consulted and employed in all times of sickness. These powwows are persons who are believed to have performed extraordinary cures, either by the applications of roots or by incantations. When an Indian wishes to be initiated into the order of the powwow, in the first place he pays a large fee to the faculty. He is then taken into the woods, where he is taught the names and virtues of the various useful plants; next he is instructed how to chant the medicine song and how to pray, which prayer is a vain repetition offered up to the Master of Life or to some munedoo whom the afflicted imagine they have offended."

Entrance to the society is obtained by a candidate applying to a member with whom he discusses the matter. If the application is favorably considered

it is then discussed with several members of the order, and in case of a favorable decision an instructor or preceptor is designated to whom he must present himself and make an agreement as to the conditions of his instruction, his fees, etc. The whole time of the student is at first not taken up and he has opportunity for hunting, fishing, and the maintenance of himself and his family. He may spend thus several years of study and preparation.

The society is graded into four degrees or periods of instruction.

The garbing of the practitioner differed according to the number of degrees which he had received in the society. Thus in the painting of the face, while acting officially:

First Degree: A broad stripe of green across the forehead and a narrow band of vermilion across the face, just below the eyes.

Second Degree: A narrow stripe of vermilion across the temples, the eyelids and the root of the nose, a short distance above which is a similar stripe of green, then another of vermilion, and above this again one of green.

Third Degree: Red and white spots are daubed all over the face, the spots of the size of the finger tips in applying the colors.

Fourth Degree: Two forms of decoration were permissible; the face was painted vermilion, with a stripe of green extending diagonally across it from the upper part of the left temporal region to the lower part of the right cheek; for the second, the face was painted red with two short, horizontal parallel bars of green across the forehead. Either of these was also employed as a sign of mourning by one whose son had been intended for the priesthood of the Midiwin.

The initiation of a qualified candidate into any of these orders was attended with very elaborate ceremonials and dignities, the recital of the history of the degree and clan. The ceremonies were usually if not always preceded by the ceremonial smoking of the pipe, and the Gods and progenitors of the degree were supposed to be invited and present usually in the form of some animal or totem believed to represent each deity or spirit. Initiation was usually celebrated during the latter part of the summer. Some at least of the ceremonies were performed in public so that the people might be duly impressed with their sacred, dignified and important nature. The main ceremonies were celebrated in a "Grand Medicine Lodge" built in an open grove or clearing, but the ritual was unintelligible to all save the initiated. The candidate was required to accurately memorize the ceremonial ritual and to transmit it in time to others, but charts were written, usually in picture writing on birch bark or skins, many of which have been preserved and studied by many students of the subject. These charts appear to me most difficult to make out or translate even with the key at hand, and of course many different interpretations have resulted.

Tobacco and other presents were furnished by the candidate, but charitable or devout members of the tribe, not participating directly were permitted to furnish gifts or contributions to the banquet and celebrations. The officiating priests were well remunerated. A specific preceptor or "docent"

was delegated to each candidate. The drums used in the ceremony were particularly constructed and consecrated. Naturally the occasions when so much highly charged "Good Medicine" was about was supposed to be particularly beneficial for the sick of the community who were expected to add of their wealth to the sacredness and dignity of the affair. Special rattles were used and the Migis, a small white shell of particularly mystical and sacred nature was extensively employed, particularly in the "Shooting of the Migis" in which the celebrant shot the spirit with the shell into the body and soul of the candidate, and the body of the sick attending the clinic. A certain amount of originality was evidently permitted the celebrants and the practitioner was allowed personal deviations as expressing his own peculiar power. The Migis shell was the sacred emblem of the society in general.

Midi Therapeutics.—During the considerable period of time in which the candidate was being instructed in the traditions, myths, songs, and ceremonies, the Midi plants were also discussed and the methods of identification, preparation, and administration of the therapeutic agents were elaborated. Specific agents and plants for definite complaints were discussed. The recognition of the complaints was necessarily mostly founded on symptoms, not on etiologic factors for little was known of this; for most, if not all diseases were believed to be of mysterious, divine, or devilish origin. In this regard it is highly probable that much of real value was further derived from the Catholic Fathers who for the time were fairly well versed in the medicine of the day; therapeutic effect was almost always attributed to the eviction of a bad spirit of some sort, and the efficiency of any method was supposed to be based on the superior knowledge or more powerful medicine of the celebrant. This did not, however, pertain to traumatic surgery in which the relation between cause and effect was fully recognized and acted upon; hence the surgery practiced was as a rule very intelligently based, and the treatments of dislocations, fractures, contusions and wounds was almost always very effectively carried out. They were skilled in massage, and in the application of active and passive movements.

Purification of the candidate was effected primarily by the sweat bath or ceremony, sometimes by the administration of cathartics and emetics. During these ceremonies the candidate was supposed to fix his mind on high and good things; he was fumigated by smoke, remained under certain taboos, as abstention from women and the like. Menstruating women were particularly supposed to injure the effectiveness and sanctity of any of these ceremonies.

In the conclusive stages mystical feats of legerdemain, sleight-of-hand, and the like to index the mystery and control which the medicine of the priests and candidates possessed. Many clever tricks were performed and just as among modern magicians the audience was not instructed as to the manner in which these seeming miracles were accomplished. Certain intimate ceremonials and instructions were carried out in private, in closed lodges and the like.

After the initiation proper had been accomplished the newly elected candidate proceeded to show his power and magic in shooting the Migis, produc-

ing syncope in his confreres, etc. The bear is a sort of tutulary spirit, the "Manido" of the society and enters largely into the mystical ceremonies.

Initiated practitioners might individually purchase from other members special songs, ceremonies, or methods which were supposed to be of particular merit; this was done outside the regular initiation ceremonies, but in the acquiring of a further degree he must gather together sufficient wealth and presents with which to endow the members of that degree. Thus certain practitioners may lead others to feel that he has a special medicine or mystery which enables the hunter to be particularly successful, to enable the lovelorn to bewitch his beloved and the like. In short, voodoo magic is quite well exemplified in many of the particular methods. Some of this "medicine" was doubtless of real value. Shrewd men of close observation of the habits of certain animals were able to impart for instance to the ambitious hunter information as to the taking of game, and the like which was the result of real keen study; most of it was probably just as valuable as the love spells and magic formulas which our young people still pay well for. A medicine man for example may from conversation with many hunters, from men of other tribes acquire a wide and valuable information as to hunting grounds, migration of animals, the methods of setting traps, and the like.

Many women took the degree of the Midiwin, but for the greater part their practice was restricted to women and children, but by no means always, if the modern practice which I have seen among the Ojibway is illustrative.

It is perhaps unnecessary to go into the details of initiation, into the various four degrees; it was largely a matter of the price and of the adeptness and personal character of the candidate. Initiation into the second degree cost twice as much as that to the first; the third degree three times; and the fourth and last degree four times as much. The "Grand Medicine Lodge" differed materially in each of the four degrees, just as it does in the conferring of the various degrees of our fraternal orders. Each degree had a chief priest, usually the senior, and on his death he was replaced by the election of a successor.

The amount of influence wielded by the Midi was general and immense, and particularly that of those who had taken the four degrees. They were believed to stand nearest to the great spirit and all the gods. A Midi Wabeno was also much dreaded because of his supposed supernatural powers.

The greatest just criticism which has been leveled against the Indian Medicine man has been because in most instances, except in traumatic surgery, which naturally played a very large part in Indian practice, of the mingled religious ceremonies with his practice; yet I have heard prayers for the sick offered up in nearly all churches and the various modern sects of our Christian faiths. Having witnessed both, I fail to find in the service of our modern faiths anything more dignified, beautiful, and worshipful than some of the chants or "dances" of the red man, conducted for the benefit of the sick, or for the purpose of imploring the assistance of their divine being in the welfare of their people. It must indeed be a very supercilious person who can fail to realize the sincerity and true devotional aspect manifested even today

in many of these ceremonies. The red man has never descended to the absurdities of Christian "Science," nor has he ever accepted anything more unscientific than the teachings of the osteopaths, chiropractors and the like, practices which are accepted by many of our wealthy, educated, and leading people. I do not believe that any flirtatious Indian girl was ever able to get away with such a story as that of Leda, of the cultured Greeks.

I feel then that we can well afford to ignore whatever of charlatinism, insincerity and faking which took place in association with Indian medical practice, since we ourselves are daily guilty of the same practices, in the universal seeking for the assistance of the mysterious, occult or religious, especially when we or ours are gravely ill. Time does not permit me to enter into this phase of medical practice or Shamanism, except to point out that our people of today practice exactly the same methods, though perhaps in a different form.

Suggestive therapeutics played a very important rôle in the practice of red medicine, just as most of us employ the same methods daily in our offices and hospitals. Many Indians were adept in the practice of hypnotism, and they employed this strange power exactly as we do today in our best psychiatric clinics. Certainly their understanding of this power was no less than that of the highly intelligent, scientifically trained Dr. Mesmer who was one of the greatest scientists of his time.

Time does not permit us to go into the matter of these ceremonies to any considerable extent, but we cannot leave this phase of our subject without reference to the Medicine Lodge and the important rôle which it plays both as a devotional observation and as a method of medical practice in practically all tribes.

The Medicine Lodge was a term commonly applied to a structure erected strictly according to many solemn ceremonials, designed to propitiate an angered or careless God or to express the spirit of humiliation, thanksgiving, or supplication, either on the part of a person or a people.

It was constructed on occasions of momentous national affairs when the whole tribe or tribes were gathered together for the purpose of council, because of some great public or personal calamity, epidemic sickness, or because of some personal complaint of so grave a nature that it was not felt that ordinary or usual priestly or medical ministration was sufficiently weighty. Even when the lodge had been built and the people and its priests gathered for the purpose of discussing some tribal or national matter, as the advisability of going to war for example, it was felt that the moment and the place was propitious for the treatment of any private physical ill.

Persons of great piety, wealth, or who, because of some personal blessing, illness, or misfortune or vow, wished to undergo the necessary expense attendant upon the building of a medicine lodge might undertake it, of course under the guidance and instruction of the chief medicine man.

Having been constructed according to the ritual, certain ceremonies, depending on the purpose of the lodge, were then performed by the medicine men after which the real object of the ceremony was reached, whether it was a council of war or for the treatment of some sick person.

Almost invariably, because of the universal employment of the sweat, either in religious or for purely medical purposes, the building of the medicine lodge was accompanied or preceded by the building of a sweat lodge, sometimes a large structure accommodating several celebrants, or a smaller one designed for but a single person at a time. At times the ceremony of sweat seems to have been carried on in the large structure, that is, in the real medicine lodge, but it appears to have been more usual that those who had been first prepared by the sweat were admitted to the ceremonials in the great lodge.

As an example of the type of chant or litany which was employed in the course of the treatment of diseases, I wish to quote the Sacred medicine formula of the Cherokees, employed by Gahuni, a famous medicine man of that tribe, in rheumatism known as "The Crippler." Gahuni died about 1855. I shall allow you to judge if it is more foolish than the mumbo of the successful quacks of today. (Seventh Annual Report, Bureau of Ethnology, 1885-86.)

"Yu! O Red Woman, you have caused it. You have put the intruder under him. Ha! Now you have come from the Sun Land. You have brought the small red seats, with your feet resting upon them. Ha! Now they have swiftly moved away from you. Relief is accomplished. Let it not be for one night alone. Let the relief come at once."

"Repeat this prayer four times. (If a woman you must say 'Red Man' and if a man, you must say 'Red Woman.') Meanwhile laying on hands, take off the hands; blow once at the fourth repetition, blow four times. And this is the medicine. Egluni (a fern), Yat na-Utsesta (Christmas fern), Ka ga Asgutage (Maiden hair fern), Da yi-Unwayi (Beavers paw). Boil the roots of six varieties together and apply the hands warm with the medicine upon them. Doctor in the evening. Doctor four consecutive nights. (The pay) is cloth and moccasins, or if he does not have them, just a little dressed deer skin and some cloth."

And this is the tabu for seven nights. "One must not touch a squirrel, a dog, a cat, mountain trout, or women. If one is treating a married man, he must not touch his wife for four nights. And he must sit on a seat by himself for four nights, and must not sit on the other seats for four nights."

Religion is always a difficult subject to discuss dispassionately. The Indian had his religion, and whatever his beliefs, he took it quite as seriously and much more faithfully than most of us do. My own private belief is that he is quite as much entitled to his beliefs as we are to ours. Whatever of brutality he may have shown has been quite equalled by many of those who profess the faith of the gentle Jew of Nazareth. As in the early days of our own medicine, religion has also been intimately mixed with the medical practices of the Indian, and this is the chief criticism which we may level against it. Psychotherapy, however, is a very important agency for cure in many, if not most diseases, and the red man has realized this perhaps more fully than we of this age do. As has been recently said by one of our leaders (Thomas Salmon), "No medical system can be complete and fully satisfactory until the proper commingling of psychotherapy with the methods of real science of pathology, chemistry, and bacteriology has been found." Until we medicine men of today have properly realized and adopted this fact, we are in no position to criticize the red prac-

titioner who did without question practice this associated psychotherapy and physical practice with notable success and well adapted to the requirements of his patients.

Naturally for an intensely religious people, the theory of disease among practically all tribes is the same, namely that of an evil spirit or bad medicine which has entered the body and caused sickness. Obviously the thing to do in that case is to drive out this evil spirit by a stronger good medicine, for which quite naturally the gods must be appealed to through proper prayers and medicines. Hence, it is that most of the incantations practiced or in vogue are such as the shooting of the Migis of the Ojibway and the sucking out of the disease which is so generally practiced not only by Indians but also by simple whites and even by animals. As is well known the medicine man in such treatments is likely to conceal in his mouth or elsewhere on his person a stone, or perhaps some living object as a cricket, frog, or the like which he dramatically produces at the proper time.

I have known of many whites who also believe in the efficacy of prayer and of divine intervention in cases of sickness. Perhaps we all are somewhat inclined in this direction to a greater or lesser degree, so why laugh at the Indian? Our church services seem quite as absurd to him, so I am told, as his ceremonies do to us.

Of course the shaman performance opens the ceremonies of the Indian to the ridicule which the superior white is likely to visit upon it, and the whole thing is then considered as a bit of charlatanism. I do not, however, agree with this conception for I am convinced that in many instances at least, the removal of the foreign body on the part of the priest has precisely the same significance as the very similar ceremonies practiced by our shamen. The attempt to deceive and willful faking is not in the mind of the respectable practitioner any more than it is in the mind of our psychiatrists when they do practically the same thing in their practice. Those of you who have seen these treatments given, cannot I am sure, have failed to note the reverential attitude with which it is usually conducted. The psychic benefit to the patient at least is real.

It is, however, a real pleasure to turn from these phases of medical practice to the methods of the Indian which commands our respect as scientists and as modern physicians.

Long before the days of Hippocrates, of Parcelius, eons before Koch, Ehrlich and Pasteur, the Indian medicine man practiced an art which came close to a science which even today commands our utmost respect and emulation.

Before Egypt was a nation, long, long before the dominance of the Greek school, Verrill with others, has shown us that the Indian medicine man practiced successfully Cesarean section, symphisiotomy; he understood and applied the wide use of trephining; he unquestionably used cocaine as an anesthetic together with other effective sedatives and analgesics; he installed dental plates and bridgework; he even supplied his patients with artificial limbs.

The writings of practically all our army surgeons shows that even the Indians of the days of Custer, Crook, and Miles well understood the treatment of fractures, dislocations, of stab and arrow wounds, and his treatment of gun-

shot wounds in the more intelligent tribes was efficient and in many respects admirable. I myself have seen something of this surgical practice. I have seen the most clever sort of splinting in fractures; I have seen ball and stab wounds well treated, the lips of bulging or gaping wounds cleverly approximated, and others have reported the use of thorns and skewers for this purpose. Shrewd and hard-headed men such as Alaes Hrdlicka, himself a skilled physician as well as one of our most eminent ethnologists and anthropologists, has spoken frequently in unstinted praise of some of these methods of surgical treatment. I have also observed as a youth much of the efficiency of pioneer medicine which owed its origin mostly to the red medicine man.

I have heard my own parents speak in terms of affection and respect of the work of Old Baptise, medicine man of the Sioux whose services were so respected and valued by the white settlers of Minnesota that when his tribe was sent to a reservation, he was asked to remain, supported by the government because of his value to the early settlements of Minnesota. I cannot say that many of the doses of "simples" which I received as a child were loved at the time by me but at least we grew up to be as healthy, sane and sound as the men and women of more advanced communities. Whatever may be said against Indian Medicine, it was also that of the pioneer in very large degree. The reports of army officers, particularly of medical officers is almost universally respectful of some at least, of the medical customs of the Indian. Furthermore almost without exception explorers, miners, settlers, and those others who have lived among the Indians have universally cited frequent instances in which strikingly successful treatments have been given by these primitive practitioners. I am certain that few of us who were born of pioneer stock or who have lived among even the modern tribes hold anything but respect for what we have seen and experienced of Red Medicine. Verrill cites, for example, his successful and comfortable recovery from yellow fever under the care of medicine men.

Let us then consider in some detail certain of the drug uses and other practices for which we are entirely dependent upon the Indian. I shall pass over these drugs very briefly, for I am confident that most of you know the more important of them. Perhaps we should put at the head of this notable list, quinine because of the great rôle which it has played not only in individual medical practice, but also because without quinine the march of civilization, great engineering and military projects must have been halted or become entirely impossible. Cocoa, with its derivative cocaine which has become so universally employed in many branches of medicine, we also owe entirely to the South American Indian. Cascara is also of Indian origin. There are many others peculiar to Indian origin, but usually in less frequent general recognition by our present-day profession. As for drugs which are universally employed, and the direct origin of which no man knows, they are very numerous. Saline laxatives were widely employed in practically all districts where nature supplied them; we might say the same for most of the wild animals also, as every field hunter knows. Foxglove, a crude form of digitalis, was widely employed in the districts where it grows. The list of laxative drugs used by the Indian is very large, and from personal experience, I can definitely say

that they are highly effective. Diuretics also are very numerous and highly efficient; mostly they are decoctions of various plants, and commonly they are administered in warm or hot water, which of course greatly increases their effect.

Emetics, now rather infrequently employed in our practice were and still are very extensively used by the Indians. Under many circumstances they were employed for religious purposes, as for example in the course of the preparation of the celebrants of the snake dance, but they are also very generally used in any manner of gastrointestinal disturbance much as we use laxatives in very many disorders, empirically. There is a tremendously large list of drugs used for the purpose of emetemisis, including large quantities of warm water and irritation of the fauces, after our own manner. Decoctions in warm water of holly, cucumber, thorowort, blood root, etc., ad infinitum. Among the Navaho the fermented urine of cayuses is used, and I am informed by an Indian trader, quite familiar with the Snake Dance ceremony, that the fermented urine of the burro is usually employed in this ceremony, supposedly because it has also some antitoxic effect against the bite of the rattlesnake.

I have found it extremely difficult to get accurate information from my Indian friends, even when they were entirely convinced of my sincerity. They are as a class very sensitive, fearful of ridicule, and most evasive in their answers to questions. I have found my most successful avenue of approach to speak as a member of the same general medical fraternity, seeking from them further information, usually telling them what I did in certain cases and asking in turn what they would do under similar circumstances. Occasionally I have been able to establish thereby a quite satisfactory relationship, but I am fully convinced that most intelligent medicine men also employ a good many valuable drugs of which we know nothing, and I am certain that scientific study of some of their preparations would be of great benefit to us. Many explorers and ethnologists have made this statement to me also.

It is quite natural that the Indian should be skilled in meeting particularly the conditions which he contacts in his ordinary life. This is shown especially in his management of snake bite. There are of course several varieties of snakes whose bite is invariably, or practically always, fatal. Against some of these reptiles they have no antidote, but I am informed by field ethnologists, explorers, miners, and the like that they are certainly able to successfully treat the bites of many supposedly highly virulent forms of snake bite. Not infrequently whites exposed to this peril have profited by this knowledge, but I have never known an Indian to divulge this secret.

The trader at Oribe who had been among the Pueblo people many years told me that he had never seen a case of fatal snake bite among those tribes to whom the snake is sacred, and yet who handle them frequently and are often bitten by them, ill-protected as they are by scanty clothing. In the famous snake dance, this same man told me that he had never known serious illness to follow the bites incurred in this ceremony although bites from the western rattler are very frequent in the chant. Of course this has been in part accounted for by the fact that for several days preceding the dance the snakes are very much disturbed and the probability is that their poison is largely exhausted by the

time of the actual ceremony. Still it is certain that of the several preparations taken before the dance, in the purification ceremonies, that antidotes are taken, whether with success or not cannot be determined. During the emetemsis which precedes the dance, the urine of the burro is taken in large quantities because of its emetic effect, and it is supposed by some that this acts also as a protectitive. They very generally in case of bites from poisonous reptiles, practice as we do, scarification and local blood letting, and this doubtless helps some, but face, neck, and arm bites are common during the dance. At least the dancer goes on with his ceremony with apparent indifference. The Indian bystanders, not participants, are certainly quite as adverse to the snakes as we are. I think that we must conclude that they do have protective measures of which we know nothing.

Febrifuges are in common use, dogwood for example, which contains cinchona in considerable quantities is so used in decoctions. My Yanqui guides in Durango, Mexico, used infusions of sarsaparilla among other preparations for this purpose, and I know from personal experience that they are effective in considerable degree.

Astringent decoctions, abstention from food, and rest are widely and successfully used in diarrhea. My Ojibway friends used a decoction of spruce or oak root for this purpose. I think each tribe has useful preparations for this purpose, depending, of course, on the plants or drugs available. My mother used fermented decoctions of wild blackberry, for example, for this purpose, and I recall that when I went away to study medicine my mother provided me with a liberal supply of this, which she had, as a pioneer woman, learned to use. It was not only effective but also very pleasant, particularly when it had sufficiently fermented. On several trips my Indian guides have supplied us with very effective preparations of like effect; but it is exceedingly difficult to get them to tell what these preparations were, notwithstanding the fact that they were certainly most kindly inclined toward me.

Very much has been said as to the immunity of Indian women from the ills peculiar to our women, of their quick and easy labors, immunity from perineal tears and the like. So far as the recent Indian is concerned, I think that these statements are incorrectly based. It is true that most Indian women do get about immediately after labor; it is also true that they very frequently have very severe obstetric difficulties as do our women. It is very true that they are stoical and indifferent to pain, for that is the custom of the people who are not given to emotional demonstrations of this kind, but from my conversations with agency doctors and from my contacts with the Indians, I am certain that they are quite as liable to difficulties of this kind as the same social types among white women, that is as compared with pioneer women, farm women and the like, but of course not comparable with women who are soft of muscle, overly fastidious, and the like. I have seen plenty of Indian women who suffered extremely from dysmenorrhea, menorrhagia, and similar conditions. I do think from my own observation and from the statements of reservation physicians that fibroma and myomas are much less frequent among them than with us. I well remember overtaking a party of Ojibway friends encamped on their way to the hunting fields because they did not wish to leave behind a favorite daughter of the chief,

who was suffering from dysmenorrhea and menorrhagia. They were as anxious as I was to get on to their hunt, but the chief told me that women were a great hindrance to tribal activities because of the troubles incident to their sex.

Malignant growths are certainly very much less frequent among the Indians than among whites. In fact they are rare among the unmixed tribes. I have never seen a malignant growth in a pure blood Indian, and reservation doctors report to me the same; it is also remarked upon by Hrdlicka. I looked into this matter last year while in Mexico, where the population is preponderately Indian. In many places tribes, like the Yaqui, have preserved to a marked degree their racial purity. Every physician with whom I came in contact made the same statement that malignant growths were exceedingly rare among the Mexican Indians. Dr. Palomeeque, a young and exceedingly brilliant surgeon, had practiced two years in the city without seeing a single instance of gastro-intestinal carcinoma in an Indian, though he had a large public charity practice. Dr. Ramon Molina, probably the leading internist of Mexico City also confirmed the same statement; and among the other physicians, including a leading pathologist, the same opinion was voiced. Hence it is that there appears to be very little knowledge among the Indians concerning newgrowths. They are certainly very rare, as is also true among pure strains of wild animals. Mr. Fenley Hunter of the Explorers Club has recently reported to me the death of a well-known squaw, Big Mary of carcinoma at Fort Yukon. The diagnosis was conformed by Dr. Hrdlicka.

The same appears to be true of thyroid disease, though I have seen simple nontoxic goiter in Indians living in the so-called thyroid districts.

Naturally rheumatism is one of the most serious diseases with which the northern tribes have to contend, the Ojibways, the Crees, and the northern tribes in general. I believe that it is rarely seen in the south, among the Pueblos, the Navahos, the Mayas, and so on. Naturally in those peoples greatly afflicted with this disease with its high disabling effect, treatments are very numerous. Perhaps in this respect they practice polypharmacy as liberally as we do in the same condition. Hot applications, the inevitable sweat bath, demulcent drinks and many decoctions are widely employed, and certain tribes use willow bark and twigs in the form of a decoction. Among the Midiwin practitioners the willow ash, which is, of course, high in the salicylates is extensively employed. I was shown its preparation by a very fine old gentleman, one of the Midiwin society of the Ojibway. This man was not only highly intelligent, but a real gentleman, if acts outweigh clothing; and he was also a most artistic and ingenious builder of the birch bark canoe, now practically obsolete. Massage, active and passive movements were employed extensively both in this disease and also in the treatment of sprains, bruises, and so on.

Anodynes and anesthetics were doubtless more extensively used and elaborated by the South American tribes, the Pre-Incas and Incas, Colimas, etc. It must always be remembered that in these sections, particularly about Lake Titicaca, an order of civilization existed which beyond doubt exceeded that of any other human race at the time of its zenith, and in many respects this persisted, though in a degenerated type, up to the time of the Spanish conquests. But our story has chiefly to do with the Indians of the times of our forefathers.

Stramonium of several kinds was used rather extensively both to quiet pain and also to produce a condition of semiintoxication in certain ceremonies. Even up to recently the government has attempted to prohibit the use of the peyote, which induced a condition of intoxication, comparable to the use of opium. Alcoholics were and still are in extensive use among the Indians of Mexico, in the form of mescal, and the favorite present-day drink in Mexico is pulque. Both these drinks, unless most artfully disguised, taste most terribly to the unaccustomed palate, but the last mentioned forms a considerable article of the diet of the ordinary Mexican. The northern tribes as a class used alcoholics very little. These preparations were very extensively employed by the tribes familiar with them, in various nervous conditions, for mental and nervous diseases were familiar enough in Indian Society. I have seen as characteristic and striking hysterical attacks among young Indians as one might wish for. As I have previously mentioned, among the members of the Midiwin, the shamans who undertook the treatment of neurologic diseases were rated in the last or highest chapter of their "Grand Medical Society." As has been noted by very many writers, mental disease was rated among the plains tribes in general as being related to the Great Spirit. These sufferers were judged as to a considerable extent irresponsible, or under the special care of the Great Mystery; hence they were treated with great kindness and consideration, a fact which was utilized, we are told, with advantage by prisoners falling into the hands of these tribes. At least we must consent that such a method of management was considerably in advance of the treatments for the insane, prevalent almost up to the time of Charcot among some Christian peoples. Our amiable ancestors of New Bedford and Salem might have taken a beneficial lesson from the red barbarians.

Treatment of contagious diseases was very badly carried out as a rule, and it is probable that in most cases it was harmful rather than otherwise, since the sweat lodge and cold plunge apparently represented the most prevalent method. It must, however, be remembered that apparently most of the epidemic contagions were introduced by the white man, typhoid fever, smallpox, measles, scarlet fever, diphtheria, and the like. Probably the less said about these matters, the better. It is quite certain, as I have said, that nearly all of these contagions whether treated by medicine men or agency physicians are terribly fatal; whole tribes within my memory have been almost wiped out by measles, for example. Darwin mentions this fact in his *Voyage of the Beagle* and even at that early day, he made a correct interpretation of its significance; for be it remembered that this great scientist had been a medical student, and that he never lost his interest in medical science.

Venereal diseases were very prevalent following the early contacts with the whites. They were for the greater part very poorly treated. This was the result of overly generous social customs, frequently mentioned for example in the voyage of Lewis and Clark. It has been told me by several well-qualified men that the southern tribes in Mexico have a plant, the Yerba Santa which is effective in syphilis. There is no doubt, I think, but that the Indian has now acquired an immunity against syphilis which is higher than that of most whites, but syphilis acquired from such infected tribes is likely to run a very malignant

course when acquired by the whites. Hrdlicka asserts with authority that there is no evidence of pre-Columbian syphilis, though the disease syphilis was spoken of variously as the "Mandan Disease," the "Gros Ventre Disease," and so on from its supposed origin from the Indian.

The subject on which I have ventured to speak to you is a most interesting one; it has pleasantly occupied much of my spare time, and has given an added interest to my trips into the wilds ever since my boyhood days. I am certain that future study of the medical customs, especially of the South American tribes and of certain of their drugs will certainly add to our armamentarium other drugs, perhaps as valuable as quinine and cocaine. The late Dr. Rusby, known to all of us for his researches along these lines frequently made this statement. Doubtless when the archeologists have found the key to the inscriptions of the Tiahunacans, the Preincas and the Incas, the Mayas and Toltecs, we shall find further evidence on medical matters of great value to the world, just as artists, sculptors, architects, economists, and students of government await anxiously positive accounts of the wonderful people who preceded us on this continent.

We may at least be certain that the medical practitioners of these people have played an important and honorable rôle in the early history of America; one which reflects honor on us who have followed them in the study and practice of the healing art. It is certainly regrettable that we have long been so blind to the great part which the prehistoric physician of America has played, and that we are still so prone to feel that in the history of progress in art, architecture, mathematics, astronomy, and even in government, we owe most to the old world while the sciences of archeology and ethnology have definitely now shown to be not in advance, but behind the early civilization of the Americas.

In my talks on this fascinating subject, I have been frequently asked for references to literature on the subject. In the hope that you may find as much pleasure and benefit in the study of this subject as I have, may I refer you first to the numerous publications of the Department of Ethnology. Get as many of the old volumes as you are fortunate enough to be able to procure. Have at hand the Encyclopedia of the American Indian. It is now old, and does not include recent discoveries, but it is most interesting none the less.* Read Schoolcraft, though he was a picturesque liar; read and study the egotistic inaccurate but fascinating and courageous story of Catlin; his plates are none the less our first artistic data on the life of the American Indian of the days of our grandfathers. Read and reread Lewis and Clark, particularly the edition of Dr. Elliot Cowes. Read Colden's *Indians,* Colonel Dodge's *The American Indian.* Read the early publications of Lieutenant Bourke. Do not forget the valuable material to be found in the Jesuit Relations, the tale of Father DeSmet; read and marvel at the story of the courageous Cabeza De Vaca, of Coronado, of Pizarro—and when your palate tires of detective stories, read the diary of Bernald Diez del Castello, the Lieutenant of Cortez. Do not forget Prescott's *Conquest of Mexico,* or his charming story of the *Conquest of Peru.*

Read the carefully compiled volume on *Shamanism* of Dr. Maddox. Gather to your choicest volumes everything original that you can find on early American history, and the records of the colonists both of our own United States and of

*A new edition is now under way.

Canada. Read Franklin's *Essay on the American Indian;* Cotton Mather. Read Schultz's *My Life as an Indian;* read every book that you can lay your hands on written by Verrill; I believe that there are only seventy-nine volumes as yet. Read the publications of Dr. Alaes Hrdlicka, the charming volume of Dr. Hough *The Hopi.* Everything written by Clark Wissler is beautifully done and most authoritative. All the publications of the American Museum on the subject are well worthy of their origin. There is a very fine little volume, recently written by Dr. Eric Stone in the series, Clio Medica, on *Medicine Among the American Indian.* Better still visit and revisit the marvelous collections of the Museum of the American Indian, Heye Foundation, the American Museum of Natural History, the choice though small, and local collection in the City Museum of Milwaukee; and you will soon find yourself equipped with a most fascinating hobby which will bring you pleasure and profit just as long as your cerebral cortex is intact. Your library will grow by leaps and bounds; you will haunt the old book stalls, and your spare change will not go to Wall Street.

Best of all, visit the Mesa Verde, Pueblo Bonito, Kitseal, Betata Kin, the still active Indian villages of Zuni, Oribi, Walpi, and the pueblo towns in general of New Mexico and of Old Mexico. Marvel in Mitla, Mont Alban, the City of Mexico with its unequalled collections and its dramatic history and startling views. And there is still Yucatan, with its preposterous and beautiful old cities, older than Egypt. There still remain for you, all of Central and South America with Cusco, Tia Huanaca, and the old Preincan and Incan towns of Peru, Bolivia, Chili—then you have started on a lifetime search of the beautiful and marvelous, on a study of the history of the country where "Columbus Came Late," but where you and I live, in a land with a history and heritage elsewhere unequalled.

59749

FUNCTIONAL STUDIES OF PATIENTS ON ANTIARTHRITIC MEDICATION

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THE primary purpose of this study was to observe the functional reaction of unselected arthritics to a few standard types of medication. Accessory modes of treatment which were based upon the etiology, and aimed at curative effect such as the elimination of foci of infection, were carried out in all cases. From the standpoint of this study, however, the latter methods were of academic interest only. The secondary purpose of this study was to observe whether, in a comparatively small series (143 cases) of arthritis, under moderate dosage of common drugs, idiosyncrasy or lack of tolerance by the kidneys or liver was frequent or the reverse.

In 1923, Worster-Drought[1] published one of the first alleged cases of phenylcinchoninic toxicity, which recovered. In somewhat desultory fashion other cases, with recovery, were reported for the subsequent three years. In 1926, Langdon-Brown[2] published one of the first* reports of a death, due to atophan. From that time to the present, there have been reported several cases of intoxication due to phenylcinchoninates. The authors appear to have overlooked the fact that not only does acute yellow atrophy arise from many causes and many drugs, but that the well-known salicylates have also been known to cause this condition.[3, 4, 5] Further, authors appear to have failed to compare the annual consumption of phenylcinchoninates and salicylates with the relative frequency of symptoms of intolerance. Since the manufacture of the former runs to almost one hundred thousand pounds, and of the latter to three million pounds† in the United States alone, it must be fairly obvious that the chance of intoxication, statistically, is slight.

There is a large bibliography on these questions of toxicity which it is scarcely necessary to cite. It seems to us that further work in the clinic, coupled with some of the newer laboratory studies, should be done to amplify the findings of the earlier writers such as Hanzlik.[22] As to the use of phenylcinchoninic acid (cinchophen) itself in these studies, we were of the opinion that the position taken by the *Journal of the American Medical Association* in 1931 was sound; and that we would, accordingly, not use phenylcinchoninic

*We consider the case reported by Cabot (Boston M. & S. J. 192: 1122, 1925) to be erroneous and so shown by the report in the J. A. M. A. 89: 1167, 1929.

†U. S. Census of Dyes and Synthetic Organic Chemicals: U. S. Tariff Commission, 1930, pp. 60, 61. Manufactured Salicylic acid 2,781,106 pounds, Cinchophen 93,765 pounds.

acid. The statement said (J. A. M. A. **97**: 409, 1931): ". . . it would be well to discontinue the use of cinchophen, or atophan, and to substitute neocinchophen for it. . . . This remarkable safety of neocinchophen is also reflected by the fact that it is practically impossible to find one undoubted case of neocinchophen liver atrophy in the literature." These facts, then, that neocinchophen and the salicylate of sodium have been so very rarely accused, led us to use these drugs in our study. We are in agreement, so far as the clinical side of the picture is concerned, with the conclusions of Davis,[7] who has recently said: "A study of 200 cases taking neocinchophen or cinchophen has been made. . . . The superiority of neocinchophen to cinchophen for general

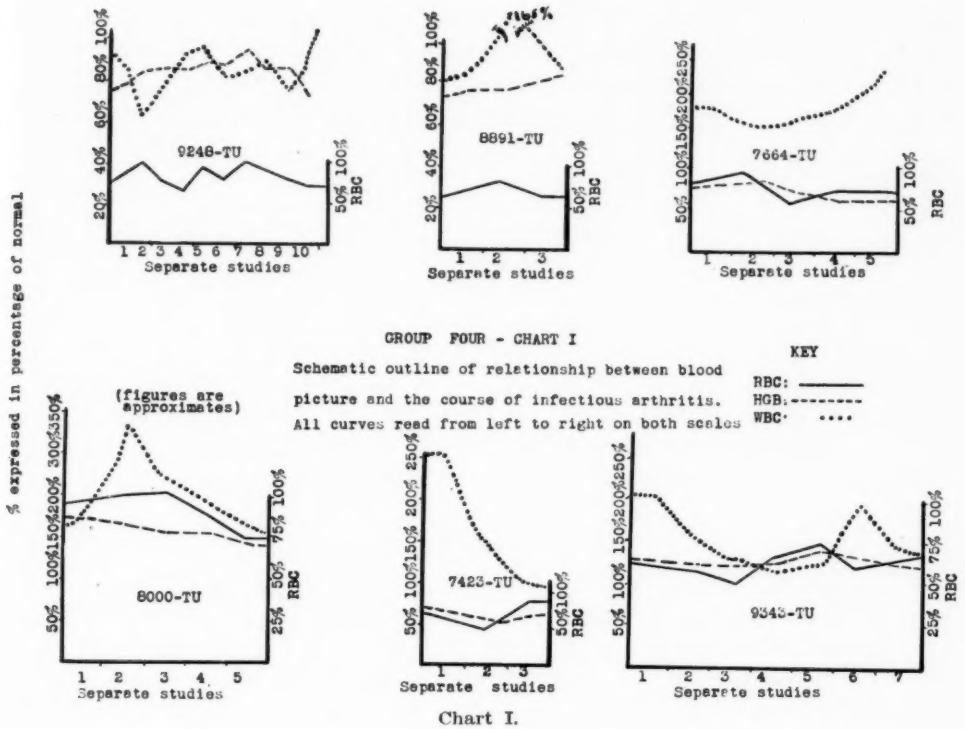


Chart I.

clinical use appears, at the present time, a fair conclusion from the evidence of the literature and the author's cases."

In the matter of nomenclature, we have been guided by the *Rheumatism Primer* published by the American Committee for the Control of Rheumatism. As they observe, no classification suits everyone or every case, but a simplified classification aids us in the comparative judgment of reported cases and hence should be adopted where possible.

Our laboratory tests* have been the classical ones as described by Hawk and Bergeim,[8] Meulengracht (Brown's modification),[9, 10] van den Bergh,[11]

*To avoid prolixity we use the quite widely recognized abbreviations of E.K.G. for electrocardiogram; B.S.P. for the bromsulphalein test; and P.S.P. for the phenolsulphonephthalein test.

Bauer,[12] Wallace and Diamond,[13] Rosenthal and White,[14] Cantarow,[15] Davies,[16] and Rowntree and Geraghty.[17]

Blood pressure studies were made on every patient; and on some patients as many as twenty or thirty determinations were made, but we found nothing of the slightest functional significance. Many blood picture studies were made, and the results in a few cases, as regards progress of the infection and secondary anemia, have been shown in Group 4 chart.

The rationale of our procedure is more clear if we consider the cases in an order inverse to the complexity of the findings. One of us (W. C. M.), seeing constantly, in his office, a considerable number of industrial cases, observed clinically, without laboratory study, 70 unselected cases of traumatic arthritis upon minimum medication of one type. The other of us (D. S.) observed similarly, at the various dispensaries to which he was attached and in his office, 50 unselected cases of arthritis, usually infectious, upon another type of medication, in minimum dosage. The first 70 case series was composed as follows:

Arthritis of the:

Feet	8 cases or 11 %
Knee	11 cases or 15½%
Ankle	5 cases or 7 %
Lumbodorsal vertebrae	5 cases or 7 %
Digits	5 cases or 7 %
Pelvis, including the sacroiliac juncture	6 cases or 8½%
Forearm, including the wrist	7 cases or 10 %
Upper arm and shoulders	4 cases or 6½%
Miscellaneous traumata about the muscles, femur, ribs, legs, etc.	19 cases or 27½%

The age distribution of these cases was as follows:

10 to 20 years	1 case
21 to 30 years	15 cases
31 to 40 years	27 cases
41 to 50 years	20 cases
51 to 60 years	6 cases
61 to 70 years	1 case

The sex distribution was: males, 67; females, 3. The youngest patient was eighteen years of age; the eldest, sixty-seven. The average length of treatment was four weeks; the shortest, one week; and the longest, twelve weeks. Every patient received 5 gr. of tolysin* three times a day. The symptomatology was affected as follows:

Moderate relief	19 cases or 27%
Marked relief	49 cases or 70%
No relief	2 cases or 3%

*A brand of paramethylphenylcinchoninic ethyl ester, manufactured by the Calco Chemical Company, Inc.; other names being used in the literature for this chemical are neocinchophen, novatophan, etc.

While laboratory studies were not done upon these patients, none at any time complained of gastrointestinal, hepatic, or renal symptoms, or showed the signs of such organic dysfunction.

In a manner roughly parallel to the above method, 50 ambulatory cases were observed by one of us (D. S.) under minimum medication with elixir sodium salicylate compound (N. F.). They received the equivalent of 5 gr. of sodium salicylate plus potassium iodide, gelsemium, cimcifuga, etc., in an alcoholic medium, three times a day. These unselected office and dispensary cases of arthritis may be anatomically subdivided as follows:

Arthritis of the:

Ankle	7 cases or 14%
Wrist and hand	6 cases or 12%
Elbow	1 case or 2%
Shoulder	6 cases or 12%
Knee	7 cases or 14%
Hip	1 case or 2%
Sacroiliac joints	3 cases or 6%
Several joints	10 cases or 38%

The ages were distributed as follows:

10 to 20 years	3 cases
21 to 30 years	4 cases
31 to 40 years	24 cases
41 to 50 years	8 cases
51 to 60 years	8 cases
61 to 70 years	2 cases
Unknown	1 case

The diagnostic classification was as follows:

Atrophic Arthritis	43 cases or 86%
Hypertrophic Arthritis	7 cases or 14%

The youngest patient was nineteen, the eldest, sixty-nine years. The sex distribution was: 38 female, 12 male. The length of treatment varied from about one week to about eight weeks, on an average four weeks.

The results obtained were:

Moderate relief	44 cases or 88%
Marked relief	3 cases or 6%
No relief	3 cases or 6%

No symptoms or signs were observed traceable to renal, gastrointestinal or hepatic dysfunction.

The above two series are obviously antithetic as regards etiology, sex, and, to a certain extent, the distribution. Nevertheless, together they cover nearly the whole range of ambulatory arthritis. In general, the symptom to be re-

TABLE I

GROUP ONE—TABLE OF CLINICAL TESTS ON THIRTEEN HOSPITALIZED UNSELECTED CASES OF ARTHRITIS

DIAGNOSIS	9248-TU HYPERTROPHIC ARTHRITIS		6675-TU ATROPHIC ARTHRITIS		10726-TU ATROPHIC ARTHRITIS		7158-TU ATROPHIC ARTHRITIS		8533-TU ATROPHIC ARTHRITIS	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
URINALYSIS	v. ft. tr. albumin, no casts	sl. tr. alb. no casts	none	ft. tr. alb. Occas. hyaline cast	no alb. no casts	v. ft. tr. alb. no casts	tr. alb. no casts	tr. alb. no casts	tr. alb. no casts	ft. tr. alb. no casts
P. S. P.	1 hr. 20% 2 hr. 30% 3 hr. 10% } 60%	1 hr. 25% 2 hr. 20% 3 hr. 11% } 56%	none	35% 24% q.n.s. } 59%	none	25% 20% 15% } 60%	1 hr. 10% 2 hr. 27% 3 hr. 32% } 69%	10% 27% 32% } 69%	1 hr. 5% 2 hr. 13% 3 hr. 7% } 25%	8% 10% 7% } 25%
B. S. P.	none	5 min. 5.0% 30 min. 0% 60 min. 0% } normal	none	0% 0% 0% } normal	none	35% 0% 0% } normal	5 min. q.n.s. 30 min. 0 60 min. 0 } 0%	q.n.s. 0% 0% } normal	none	25% 0% 0% } normal
Van Den Bergh	Direct: neg. Indirect: <0.2 mgs.	Direct: neg. Indirect: <0.3 mgs.	none	Direct: neg. Indirect: <0.5 mgs.	none	Direct: neg. Indirect: <0.2 mgs.	none	none	Direct: neg. Indirect: <0.2 mgs.	none
Icterus Index	7.0	8.0 (avg.)	none	4.0	none	9.0	3.0	6.0	5.0	none
Wassermann	negative	none	negative	none	negative	none	negative	none	anticomplementary	none
Kahn Reaction	negative	none	negative	none	negative	none	negative	none	negative	none
Blood Chemistry	Urea-N. 15.5	none	Urea-N.: 15.5 Uric Ac.: 4.1 Creat.: 1.4 Dextrose: 129.8	none	none	none	Urea-N.: 18.0 Uric Ac.: 3.7 Creat.: 1.4 Dextrose: 119.0	none	Urea-N.: 36.0 Uric Ac.: 3.8 Creat.: 2.1 Dextrose: 88.0	none
Galactose Test	none	1.5 gms. /5 hr.	none	2.3 gms. /5 hr.	none	2.3 gms. /5 hr.	1.5 gms. /5 hr.	1.5 gms./5 hr.	none	0.435 gms. /5 hr.
Urobilinogen	none	1:10 neg. 1:20 neg.	none	1:10 pos. 1:20 neg.	none	1:10 pos. 1:20 neg.	1:10 pos. 1:20 pos.	1:10 pos. 1:20 pos.	none	1:10 pos 1:20 neg.
Blood Count	(See Chart I)	(See Chart I)	RBC: 4790000 WBC: 11700 Hb: 78%	none	none	none	none	none	RBC: 3360000 WBC: 11750 Hb: 69%	none

Tolysin medication—30 gr./day

TABLE I—Continued

DIAGNOSIS	8891-TU ATROPHIC ARTHRITIS ACUTE TONSILLITIS		1450-LK ATROPHIC ARTHRITIS		947-LK ATROPHIC ARTHRITIS		1027-LK ATROPHIC ARTHRITIS		1127-LK ATROPHIC ARTHRITIS	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
URINALYSIS	sl. tr. alb. no casts	sl. tr. alb. occas. hyl. cast	none	neg. alb. no casts or cells	no alb. no casts	ft. tr. alb. no casts	no alb. no casts	tr. alb. no casts	none	ft. tr. alb. no casts
P. S. P.	1 hr. 25% 2 hr. 30% 60% 3 hr. 5%	1 hr. 28% 2 hr. 30% 76% 3 hr. 18%	none	1 hr. 12% 2 hr. 12% 32% 3 hr. 8%	1 hr. 35% 2 hr. 25% 75% 3 hr. 15%	1 hr. 20% 2 hr. 20% 58% 3 hr. 18%	1 hr. 35% 2 hr. 15% 60% 3 hr. 10%	1 hr. 30% 2 hr. 20% 65% 3 hr. 15%	none	1 hr. 5% 2 hr. 15% 45% 3 hr. 25%
B. S. P.	5 min. 5% 30 min. 0% nor- 60 min. 0% mal	5 min. 28% 30 min. 0% nor- 60 min. 0% mal	5 min. 80% 30 min. 0% nor- 60 min. 0% mal	5 min. 85% 30 min. 0% nor- 60 min. 0% mal	none	none	none	none	none	5 min. 80% 30 min. neg. nor- 60 min. neg. mal
Van Den Bergh	Direct: neg. Indirect: <0.2 mg.	Direct: neg. Indirect: <0.2 mg.	none	none	none	none	none	none	none	none
Icterus Index	4.0	4.0	none	5.5	3.0	4.0	4.5	8.0	none	5
Wassermann	negative	negative	doubtful	negative	none	negative	negative	none	negative	none
Kahn Reaction	negative	negative	doubtful	negative	none	negative	negative	none	negative	none
Blood Chemistry	Urea-N: 16 Creatin: 1.2 Uric Ac.: 4.84 Dextrose: 118.0	none	none	Urea-N: 6 Dextrose: 90	none	Cholesterol 180	Urea-N: 19 Dextrose: 90	Urea-N: 11 Dextrose: 90	none	Urea: 11 Dextrose: 90 Creatin: 1.8 Calcium: 9.0
Galactose Test	none	none	none	none	none	none	none	none	none	none
Urobilinogen	none	none	none	none	none	none	none	none	none	none
Blood Count	RBC: 3550000 WBC: 5050 Hb: 75%	RBC: 3400000 WBC: 5250 Hb: 78%	none	RBC: 4520000 WBC: 7700 Hb: 85%	none	none	none	none	none	RBC: 4040000 WBC: 5000 Hb: 80%

Tolysin medication — 30 gr./day

TABLE I—Continued

DIAGNOSIS	7664-TU ATROPHIC ARTHRITIS		7423-TU ATROPHIC ARTHRITIS		9836-TU ATROPHIC ARTHRITIS ENDOCRINE DYSCRASIA	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
URINALYSIS	ft. tr. alb. no casts	v. ft. tr. alb. no casts	t. tr. alb. no casts	ft. tr. alb. no casts	ft. tr. alb. no casts	no alb. no casts
P. S. P.	1 hr. 4% 2 hr. 3% 3 hr. 28% 35%	1 hr. 5% 2 hr. 12% 3 hr. 10% 27%	none	1 hr. 30% 2 hr. 30% 3 hr. 15% 75%	none	1 hr. 30% 2 hr. 25% 3 hr. 18% 73%
B. S. P.	5 min. none 30 min. neg. 60 min. neg. normal	5 min. q.n.s. 30 min. 0% 60 min. 0% normal	none	none	none	5 min. 30% 30 min. neg. 60 min. neg. normal
Van Den Bergh	Direct: neg. Indirect: <0.5 mg.	none	none	none	none	Direct: neg. Indirect: <0.2 mg
Icterus Index	6.0	4.0	4.0	4.0	none	6.0
Wassermann	negative	none	negative	none	negative	none
Kahn Reaction	negative	none	negative	none	negative	none
Blood Chemistry	Urea-N: 19 Uric Ac.: 3.4 Creatin: 1.4 Dextrose: 135	none	Urea-N: 14 Creatin: 1.13 Uric Ac.: 2.6 Dextrose: 124	none	none	Urea-N: 9 Uric Ac.: 3.6
Galactose Test	10 gm./5 hr.	13.8 gm./5 hr.	none	2.6 gm./5 hr.	none	1.96 gm./5 hr.
Urobilinogen	conc. positive 1:10 negative 1:20 negative	1:10 positive 1:20 negative	none	conc. positive 1:10 positive 1:20 negative	none	1:10 positive 1:20 negative
Blood Count	none	none	none	none	none	none

Tolysin medication—30 gr./day

lieved by medication, pending the institution of curative processes by nature and the physician, was pain. It is remarkable that, with the very small doses employed, only 3 per cent, and about the same in each series, were not relieved. The medication was obviously minimal in both series and apparently satisfactory. No toxicity was expected or observed.

It seemed to one of us (D. S.) that further, more detailed studies with extensive laboratory functional tests were indicated at higher dosage levels. Accordingly, a series of 23 cases, drawn from the wards of Temple University Hospital and Lankenau Hospital was studied quite carefully. It should be

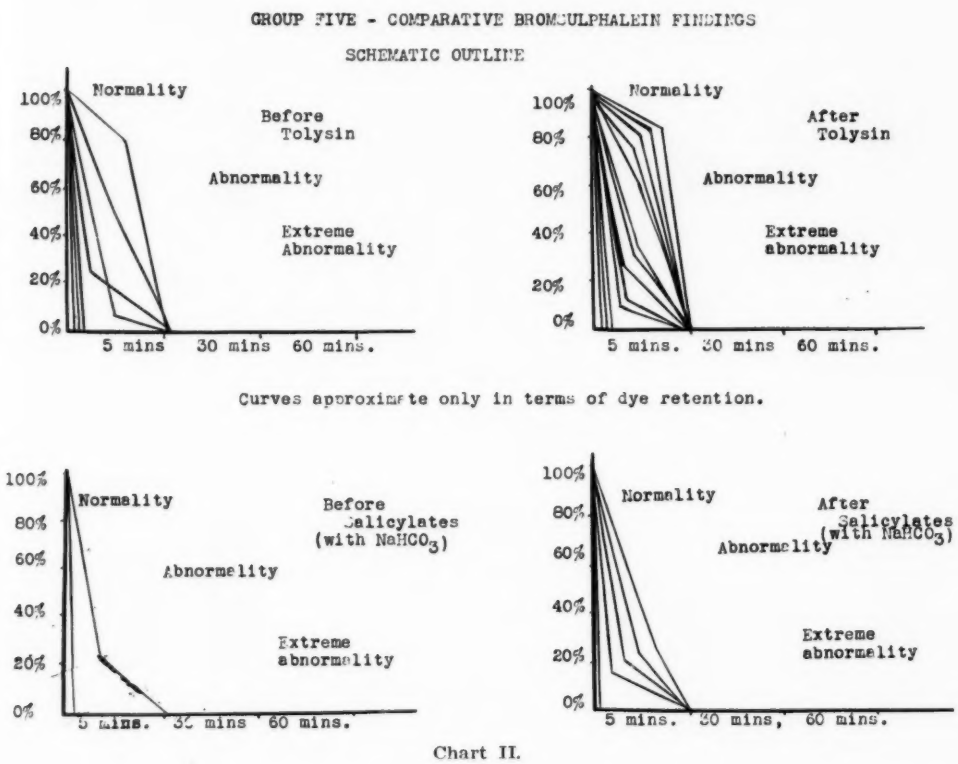


Chart II.

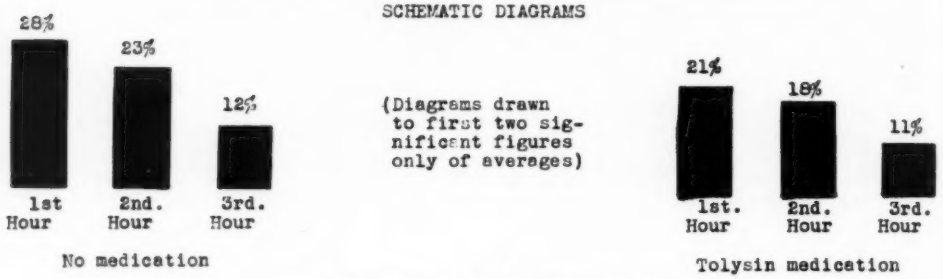
noted that this series was studied not for relief of pain, or for associated phenomena in arthritis, but principally to learn something of the organic functional response of arthritic patients to antirheumatic medication. To give the complete history and physical examination on each of these cases, in addition to the laboratory results, would consume entirely too much space; in fact, it is impossible to more than approximate the laboratory findings after medication was instituted. Almost 600 special laboratory, x-ray, blood pressure, and consultation examinations were made on the 23 cases. It must be pointed out that, in the tables subjoined, the tests representing work done during or after medication are always taken as the worst or least favorable test; and usually

represent three or more tests during that period upon that particular function. We have tabulated the laboratory findings in brief as follows:

Group I	13 cases under tolysin medication
Group II	5 cases under minimal salicylate and iodide medication
Group III	5 cases under standard salicylate and sodium bicarbonate medication
Group IV	Significant blood findings
Group V	Comparative B.S.P. findings
Group VI	Comparative P.S.P. findings

GROUP SIX -COMPARATIVE PHENOLSULPHONEPHTHALEIN FINDINGS

SCHEMATIC DIAGRAMS



Averaged readings on 74 separate tests.

Chart III.

DISCUSSION OF TABULATED CASES

It will be noted in all the tables that it was impossible, due to the exigencies of hospital routine, to do every test upon every patient. Many more tests were done after, or during, medication than before. A consideration of all the findings gives at least temporary answer, however, to the question of the extent to which renal and hepatic functions are affected by standard moderate medication under the conditions of the study. On an average, three functional studies of the P.S.P., B.S.P., and icterus index were done for each one reported in the tables; but the graphic charts are inclusive of nearly all. An interesting point was that nearly all cases of arthritis due to infection show traces of albumin in the urine either before or after treatment, or both.

Case 9248.—T. U. (Table I), is interesting in that the case was clearly one of slightly impaired renal and hepatic function evidenced by the slightly raised icterus index and slightly subnormal P.S.P., and one positive indirect van den Bergh. Yet, under three weeks' medication with tolysin, the patient showed no significant change in the functional indices. Case 10726, T. U., showed a slightly raised icterus index, but no other signs. Case 7158, T. U., had all the evidence of focal infection over many years; but the E.K.G. did not reveal any wave abnormality; and the laboratory findings were normal. Case 8533, T. U., was of typical rheumatic origin. The heart was enlarged and there was an insufficiency of the mitral valve. E.K.G. showed extrasystoles and left axis deviation. The P.S.P. in this case was consistently low; but all other tests were approximately normal. On Case 8891, T. U., we did a *Mosenthal* test and found an ability to concentrate that was definitely diminished; yet the blood chemistry, P.S.P., and urinalysis showed insignificant changes. Liver function tests in the case were entirely normal. Case 1450, L. K., showed consistently low and declining P.S.P. without any other significant findings except a Wassermann and Kahn reaction first reported positive, then negative. In Case 1027, L. K., it was interesting to correlate the declining blood urea nitrogen with a rising P.S.P. output, the liver function test being essentially normal. Case 7664, T. U., showed definite progressive diminution in function of the kidney by P.S.P. test; but the icterus index improved while the galactose test was, and remained, poor, suggesting a renal factor. Case 7423, T. U., showed normal function test, a normal E.K.G., but a typical rheumatic history and was, in fact, a typical case of rheumatic disease. All of the above cases were treated, so far as analgesic medication was concerned, with 10 gr. of tolysin three times a day. So far as could be noted, there were no evidences of significant change in the laboratory tests after medication.

Group II cases were treated (Table II) upon a complex and somewhat irrational mixture known as elixir sodium salicylate, compound (N. F.) in amounts which would give a dose of about 18 gr. of the salicylate and 3½ gr. of KI per day. At first it was thought to use a placebo in these cases; but the presence of a very small amount of the salicylate in the mixture gave it some effect and satisfied the patients. Case 863, L. K., was an interesting one because of the absolutely negative findings in the liver function test in the presence of clear abnormality elsewhere. Here the P.S.P. declined progressively; focal infection was obviously present in the tonsils; the blood urea nitrogen was definitely raised; yet the urine did not show much albumin and no sugar despite a very definite hyperglycemia. The case strikingly demonstrated the advisability of blood dextrose determinations in such cases. Case 1329, L. K., is interesting because, on physical examination, the liver was found considerably enlarged. The functional tests were, without exception, normal. Case 1122, L. K., is worth consideration since it was the only one in the series of 23 hospital cases in which a definitely abnormal B.S.P. was found after mild medication. Seven days later, however, the B.S.P. was normal as

TABLE II

GROUP TWO—TABLE OF CLINICAL TESTS ON FIVE HOSPITALIZED UNSELECTED CASES OF ARTHRITIS

DIAGNOSIS	863-LK HYPERTROPHIC ARTHRITIS		1329-LK HYPERTROPHIC ARTHRITIS		1122-LK HYPERTROPHIC ARTHRITIS		1179-LK HYPERTROPHIC ARTHRITIS		1112-LK ATROPHIC ARTHRITIS	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
URINALYSIS	v. ft. tr. alb. no casts	no alb. no casts	none	no alb. no casts	none	none	none	no alb. no casts	no alb. no casts	v. ft. tr. alb. no casts
P. S. P.	1 hr. 60% 2 hr. 18% 3 hr. 2% } 74%	1 hr. 15% 2 hr. 15% 3 hr. 14% } 44%	1 hr. 40% 2 hr. 30% 3 hr. 18% } 88%	1 hr. 30% 2 hr. 20% 3 hr. 20% } 70%	1 hr. 50% 2 hr. 20% 3 hr. 6% } 76%	1 hr. 40% 2 hr. 22% 3 hr. 12% } 74%	none	1 hr. 18% 2 hr. 20% 3 hr. 8% } 46%	1 hr. 32% 2 hr. 27% 3 hr. 20% } 79%	1 hr. 30% 2 hr. 20% 3 hr. 10% } 60%
B. S. P.	5 min. 35% 30 min. 0% 60 min. 0% } normal	5 min. 45% 30 min. neg. 60 min. neg. } normal	none	5 min. 100% 30 min. neg. 60 min. neg. } normal	5 min. q.n.s. 30 min. 0% 60 min. 0% } 7%	5 min. 50% 30 min. 20% 60 min. 0% } partially abnormal	none	5 min. 95% 30 min. neg. 60 min. neg. } normal	none	5 min. 90% 30 min. neg. 60 min. neg. } normal
Van Den Bergh	none	none	none	none	none	none	none	none	none	none
Icterus Index	none	5.5	none	4.5	none	5.5	none	4.5	7.0	4.0
Wassermann	anticomplementary	negative	none	negative	none	negative	negative	none	four plus	plus 4
Kahn Reaction	negativ e	negative	none	negative	none	negative	negative	none	one plus	plus 2
Blood Chemistry	Urea-N: 30 Dextrose: 190.0	Urea-N: 24 Dextrose: 165	none	Urea-N: 18 Dextrose: 95	Dextrose: 70	Cholesterol: 250	none	none	Urea-N: 6 Dextrose: 95 Creatin: 1.4 Chlorides: 440 Cholesterol: 320	Dextrose: 95
Galactose Test	none	none	none	none	none	none	none	none	none	none
Urobilinogen	non	none	none	none	none	none	none	none	none	none
Blood Count	RBC: 4040000 WBC: 6600 Hb 75%	RBC: 4320000 WBC: 6800 Hb: 80%	none	RBC: 4080000 WBC: 6800 Hb: 80%	none	none	none	RBC: 4480000 WBC: 6000 Hb: 85%	none	none

Sodium Salicylate about 18 gr. plus KI about 3½ gr.

TABLE III

GROUP THREE—TABLE OF CLINICAL TESTS ON FIVE HOSPITALIZED UNSELECTED CASES OF ARTHRITIS

DIAGNOSIS	8000-TU ATROPHIC ARTHRITIS BEFORE	8000-TU ATROPHIC ARTHRITIS AFTER	8529-TU ATROPHIC ARTHRITIS BEFORE	8529-TU ATROPHIC ARTHRITIS AFTER	9343-TU ATROPHIC ARTHRITIS BEFORE	9343-TU ATROPHIC ARTHRITIS AFTER	9836-TU ATROPHIC ARTHRITIS BEFORE	9836-TU ATROPHIC ARTHRITIS AFTER	5693-TU ATROPHIC ARTHRITIS BEFORE	5693-TU ATROPHIC ARTHRITIS AFTER
URINALYSIS	v. ft. tr. alb. no casts	v. ft. tr. alb. no casts	v. sl. tr. alb. no casts	v. ft. tr. alb. no casts	v. sl. tr. alb. no casts	v. sl. tr. alb. no casts	ft. tr. alb. no casts	v. ft. tr. alb. no casts	none	none
P. S. P.	1 hr. 54% 2 hr. 32% 3 hr. 2% } 88%	1 hr. 47% 2 hr. 27% 3 hr. 12% } 86%	1 hr. 78% 2 hr. 78% 3 hr. 13% } 91%	1 hr. 7% 2 hr. 40% 3 hr. 18% } 65%	1 hr. 30% 2 hr. 35% 3 hr. 10% } 75%	1 hr. 27% 2 hr. 8% 3 hr. 17% } 52%	1 hr. 12% 2 hr. 17% 3 hr. 15% } 44%	1 hr. 12% 2 hr. 16% 3 hr. 12% } 40%	none	none
B. S. P.	none	none	none	5 min. 20% 30 min. neg. 60 min. neg. } normal	none	5 min. 25% 30 min. neg. 60 min. neg. } normal	none	5 min. 25% 30 min. neg. 60 min. neg. } normal	none	norma
Van Den Bergh	none	none	none	negative <0.2 mg.	negative <0.2 mg.	negative <0.2 mg.	none	negative <0.2 mg.	negative <0.2 mg.	negative <0.2 mg.
Icterus Index	4.0	6.0	none	6.0	3.0	5.0	9.0	4.0	3.0	3.0
Wassermann	negative	negative	negative	none	negative	none	negative	none	none	none
Kahn Reaction	negative	negative	negative	none	negative	none	negative	none	none	none
Blood Chemistry	none (Basal metab. minus 15)	none (Basal metab. minus 8)	Urea-N: 14.8 Uric. Ac.: 2.6 Creatin: 1.3 Dextrose: 104 Cholesterol 260	none	Urea-N: 12 Creatin: 1.6 Uric. Ac: 4.3 Dextrose: 132 Cholesterol 290	none	Urea-N: 13 Creatin: 1.3 Uric Ac.: 2.7 Dextrose: 80	Urea-N: 13 Creatin: 1.2 Uric Ac.: 2.5 Dextrose: 82	Urea-N: 18 Creatin: 1.8 Uric Ac.: 3.0 Dextrose: 139	Urea-N: 18 Creatin: 1.8 Uric Ac.: 3.0 Dextrose: 139
Galactose Test	none	none	none	none	none	none	none	1.306 cms./5 hr.	none	none
Urobilinogen	none	none	none	none	none	none	none	none	none	none
Blood Count (last)	RBC: 4780000 WBC: 10500 Hb: 87%	RBC: 4260000 WBC: 9750 Hb: 72%	none	none	RBC: 2990000 WBC: 12950 Hb: 63%	RBC: 3320000 WBC: 8750 Hb: 63%	none	none	none	none

Average dose Sodium Salicylate 80 gr./day. Sodium Bicarbonate 80 gr./day

TABLE IV

GROUP FIVE. BROMSULPHALEIN TEST

(Before Tolysin): CASE	DATE	RETENTION AT END OF 5 MIN.	30 MIN.	60 MIN.
TU 7158	5/11/32	q.n.s.	neg.	neg.
TU 8533	8/29/32	25%	neg.	neg.
TU 8891	7/15/32	5%	neg.	neg.
LK 1450	1/14/33	80%	neg.	neg.
TU 7664	5/ 3/32	q.n.s.	neg.	neg.
(After Tolysin):				
TU 9248	8/16/32	50%	neg.	neg.
TU 6676	5/ 7/32	q.n.s.	neg.	neg.
TU 10726	11/ 2/32	35%	neg.	neg.
	11/ 9/32	8%	neg.	neg.
TU 7158	5/24/32	q.n.s.	neg.	neg.
TU 8891	8/ 5/32	28%	neg.	neg.
LK 1450	1/20/33	85%	neg.	neg.
	1/27/33	5%	neg.	neg.
	2/ 3/33	8%	neg.	neg.
LK 1127	1/ 4/33	85%	neg.	neg.
	1/11/33	75%	neg.	neg.
	1/18/33	60%	neg.	neg.
	1/25/33	80%	neg.	neg.
TU 7664	5/18/33	q.n s.	neg.	neg.
TU 9836	11/12/32	30%	neg.	neg.
(Before Sodium Salicylate and Sodium Bicarbonate):				
none	none	none	none	none
(After Sodium Salicylate and Sodium Bicarbonate):				
TU 8000	7/25/32	15%	neg.	q.n.s.
	8/ 1/32	20%	neg.	q.n.s.
TU 9343	7/15/32	25%	neg.	q.n.s.
	8/ 5/32	18%	neg.	q.n.s.
TU 9836	8/30/32	25%	neg.	neg.
TU 5693	5/ 5/32	q.n.s.	neg.	neg.
	5/18/32	q.n.s.	neg.	neg.
(Before Sodium Salicylate Mixture):				
LK 863	12/16/32	35%	neg.	neg.
LK 1122	12/16/32	q.n.s.	neg.	neg.
(After Sodium Salicylate Mixture):				
LK 863	12/23/32	neg.	neg.	neg.
	12/30/32	45%	neg.	neg.
	1/ 6/33	30%	neg.	neg.
LK 1329	1/11/33	85%	neg.	neg.
	1/18/33	100%	neg.	neg.
	1/25/33	95%	neg.	neg.
LK 1179	12/28/32	80%	80%	neg.
	1/ 4/33	90%	neg.	neg.
	1/11/33	90%	neg.	neg.
	1/18/33	60%	neg.	neg.
	1/25/33	95%	neg.	neg.
LK 1112	12/23/32	85%	neg.	neg.
	12/28/32	50%	neg.	neg.
	1/ 8/33	90%	neg.	neg.
	1/11/33	90%	neg.	neg.
LK 1122	12/23/32	50%	20%	neg.
	12/30/32	80%	neg.	neg.

were all other tests at all times; and as a consequence the significance of the findings, if any, cannot be determined. Case 1179, L. K., had several interesting features, including an abnormal B.S.P. became normal after a few days' stay in the hospital; a consistently low P.S.P. unassociated with albumin or casts in the urine; and a normal icterus index with improving B. S. P. It was interesting to note that during this period his liver, by physical signs, progressively enlarged. We offer no explanation. This single group was, in a loose sense, a control group. Nothing abnormal was expected or noted.

Group III (5 cases) represented standard dosage with sodium salicylate and sodium bicarbonate, antiarthritic medication widely recognized in hospitals. All of these cases showed one or more interesting points. All had a definite rheumatic fever history and in all the diagnosis of acute rheumatic fever was justified. None showed any significant change in laboratory findings under the above medication, and particularly was the liver function free from such change. In three cases there was a definite trend downward (rather than upward as claimed by the protagonists of sodium bicarbonate) in the P.S.P. test (Cases 8529, T. U.; 9343, T. U.; 9836, T. U.), but this change was commonly later reversed. The E.K.G. findings showed cardiac involvement in two cases (Cases 8000, T. U., 5693, T. U.).

The subject of blood studies has not been mentioned up to this point, but in these 23 cases some blood work was done on each, and a great deal of work was done on many. In some, the so-called "Schilling hemogram" was constructed to indicate comparatively the complete count (repeated from five to ten times) together with an estimate of the shift in the nuclear structure of the white cells "to the left" or "to the right." In this regard we have been very much interested in the recent publication by Steinbrocker and Hartung[18] on the "filament-nonfilament count" of arthritis as an aid in differential diagnosis. We have scarcely space to go into an analysis of these cases as viewed from such an angle, but hope to be able to do so in a subsequent publication. Solely to illustrate the constant tendency to hypochromic anemia in these cases, we have appended a few rough diagrammatic charts of the course of the red cells, hemoglobin and white count. It is our preliminary opinion that the hypochromic anemia, which almost invariably occurs in these cases, is best treated when infection is quiescent and hemolysis has ceased.[23] We should like to call attention to the article by Robertson, Swalm, and Konzelmann[19] in which an excellent summary of liver function tests is given. We have made no attempt to use the recently suggested Lichtman[20] test of hepatic function because of the difficulty of obtaining betahydroxyphenylcinchoninic acid for the preparation of standards.

SUMMARY

No essential difference was noted in the clinical response of 120 unselected cases of arthritis to minimal doses of tolysin or sodium salicylate in grain-for-grain equivalent dosage. The presence of potassium iodide, cimicifuga, gel-

semium, and such medicaments did not seem to add to, or detract from, the effects noted.

The thirteen cases under 30 gr. of tolysin daily, carefully studied upon hospital wards, showed no signs of liver involvement which could be confirmed by any of the common laboratory functional tests frequently repeated, and the kidney signs were in conformity with the usual findings of a slight albuminuria in arthritis regardless of medication. In this matter, our experience coincides with that of Chace, Myers and Killian[21] who remarked over ten years ago, after careful study: "In the cases which we employed, neither cinchophen nor neocinchophen produced proteinuria or intensified it when already present. . . ."

The series of five cases upon very small doses of salicylates (Group II) failed to differ materially from any of the others from a laboratory standpoint.

The series of five cases upon standard salicylate medication averaging more than 80 gr. of sodium salicylate per day (Group III) together with sodium bicarbonate, differed not at all from the preceding cases in the character of their functional tests.

The entire study failed to show any effects of so-called toxicity from antirheumatic medication in moderate or small dosage during the period of study and with the dosages employed. We wish at this point to express our great appreciation to Doctors Robertson, Konzelmann, Kline and Bortz for their cooperation; and to Miss Schubert and Miss Hohl for assistance in the pathologic work.

CONCLUSIONS

1. Moderate dosage of tolysin and sodium salicylate with bicarbonate, produced no appreciable changes in the laboratory tests for total renal and hepatic function in arthritic cases under the conditions of our study.

2. Hypochromic anemia is an almost constant concomitant of acute and chronic nontraumatic arthritis.

3. The widely accepted treatment of arthritis, involving accurate diagnosis; antietiologic measures; anatomic, physiologic and psychic rest; the regulation of bodily and endocrine chemistry, is best charted and checked by careful functional laboratory studies.

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A STUDY OF THE OTTO TEST FOR STRYCHNINE*

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ONE of the earliest tests devised for the detection of the presence of strychnine was proposed by Otto[1] in 1846. This test consists of treating a small quantity of strychnine with a few drops of concentrated sulphuric acid. When a small crystal of potassium dichromate is moved about in this liquid a deep violet color changing to a dirty green is produced.

A study in this laboratory[2] has shown that the Mandelin test for strychnine is given by a number of substances other than strychnine. A study was therefore undertaken in order to determine whether or not the Otto test was more specific for strychnine than was the Mandelin test.

A record has been made of a number of substances which produce a color similar to that given by strychnine with H_2SO_4 – $K_2Cr_2O_7$. Wormley[3] states that curarine and cod liver oil give a similar test. Witthaus[4] lists geissospermin as giving the same test as strychnine, while aniline at first gives the test but soon changes to a black. A number of substances are listed by Wormley[3] which will interfere with the test. These include morphine, quinine, sugar, brucine, and tartar emetic.

In working with crude drugs, Fuller[5] has found that the petroleum ether residues from gelsemium and yohimbe give the strychnine test.

Mameli[6] made a study of the interference of certain substances employed in therapeutics on the Otto color reaction. He found a number of drugs which more or less interfered with the test. The amounts of the drugs used in the tests, however, were not given.

PROCEDURE

Preparation of Solutions to Be Tested.—The organic compounds used in this investigation were prepared in the proper solvent so that 1 c.c. was equivalent to 1 mg. of the compound. The strychnine solution was of the same strength.

Procedure of the Tests.—Three tests were made on each compound. For the first, 1 c.c. of the solution of the organic compound was evaporated and the usual test was made and any color noted. The second test was made in the same manner except that 1 c.c. of strychnine was evaporated with the same volume of the organic compound and the test made on the mixture. The third test was carried out as above, except that 5 c.c. of the impurity were mixed with the strychnine.

The results of the tests when the organic compounds were tested alone are given in the pages which immediately follow: The name is given first and directly opposite is given the color reaction.

*From the University of Colorado.
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ALKALOIDS AND ALKALOIDAL SALTS

Organic Substances	*Color Reaction*
Apomorphine	Brownish green
Berberine	Brown to black
Brucine	Orange
Colchicine	Orange, acid alone
Cotarnine hydrochloride	Orange
Cryptopine	Violet, acid alone
Delphinine	Reddish brown, acid alone
Gelseminine	Reddish brown
Hydrastine	Yellow, trace of violet
Papaverine	Light violet, acid alone
Piperine	Violet brown
Sanguinarine nitrate	Greenish black, acid alone
Solamine	Yellow, acid alone
Strychnine	Violet to blue to orange
Veratrine	Orange to red, acid alone

No Color Reaction.—Aconitine, atropine, belladonnine, caffeine, cinchonidine, cinchonine, cocaine, codeine, daturine, dionine, emetine, ergotine, beta-eucaine hydrochloride, heroine, homatropine, hyoscyamine, morphine, narceine, nicotine, pelletierine, phenacaine, physostigmine, pilocarpine, pseudopelletierine, quinidine, quinine, scopolamine, sparteine, theobromine, theophylline.

AMINO ACIDS AND DERIVATIVES

Glycyltryptophane	Dirty green
Phenylglycine	Violet brown
Tryptophane	Dirty green, trace purple

No Color Reaction.—Acetylphenylglycine, alpha-alanine, para-aminophenylglycine, arginine, asparagine, aspartic acid, *dl*-benzoylalanine, betaine hydrochloride, creatine, creatinine, diiodotyrosine, edestine, ethylglycollate, glutamic acid, glycine, hippuric acid, isoleucine, leucine, para-nitrophenylglycine, alpha-phenylalanine, beta-phenylalanine, tyrosine, *dl*-valine.

ALIPHATIC ACIDS

No Color Reaction.—Aconitic acid, adipic acid, *dl*-alpha-aminoacetylacetic acid, alpha-bromopropionic acid, beta-bromopropionic acid, formic acid, fumaric acid, levulinic acid, maleic acid, malic acid, malonic acid, mesaconic acid, mucic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, tartronic acid, trichloracetic acid.

ALIPHATIC ACID SALTS, ESTERS, AND DERIVATIVES

No Color Reaction.—Ethyl oxalate, ethyl succinate, isoamyl propionate, isobutyl acetate, isobutyl isothiocyanate, methyl isothiocyanate, sodium formate, sodium oxalate, thallous formate, thallous malonate, triacetin, tributyrin.

ALIPHATIC ALCOHOLS AND KETONES

No Color Reaction.—Acetylacetone, cetyl alcohol, dulcitol, erythritol, ethylene glycol, isobutyl alcohol, isopropyl alcohol, mannitol, melissyl alcohol, methyl heptenone, octyl alcohol, phorone, trichlorobutyl alcohol.

SUGARS

No Color Reaction.—Arabinose, galactose, glucose, lactose, levulose, maltose, *d*-mannose, melezitose, raffinose, rhamnose, sucrose, xylose.

UREA AND URIC ACID DERIVATIVES

Allylphenylthiocarbamide	Brown, streaks of violet
Amytal (isoamylethylbarbituric acid)	Light green
Triphenylguanidine	Brown to green

No Color Reaction.—Allylthiocarbamide, allylthiourea, acetylmethylurea, allantoine, alloxantine, barbital (diethylmalonylurea), barbituric acid, biuret, *dl-n-* butylthiourea, dibromobarbituric acid, diphenylthiourea, guanine hydrochloride, ipral (calcium ethylisopropylbarbiturate), luminol (phenylethylbarbituric acid), peralga (aminopyrinediethylbarbiturate), thiobarbituric acid, thiourea, urea, urethane, uric acid.

GLUCOSIDES

Aesculin	Brown, trace violet
Arbutin	Reddish violet, acid alone
Colocynthin	Yellow, acid alone
Digitalin	Reddish brown, acid alone
Salicin	Magenta, acid alone
Saponin	Brown, acid alone

No Color Reaction.—Amygdalin, convallamarin, elaterin, phloridzin, picrotoxin, santonin.

MISCELLANEOUS ALIPHATIC COMPOUNDS

Oenanthol	Green

No Color Reaction.—Acetal, acetaldoxime, acetamide, acetoxime, aldehydeammonia, aminoguanidine bicarbonate, bromoform, ter-butyl bromide, chitin, chloral hydrate, chloral urethane, chloropicrine, dimethylglyoxime, hexachloroethane, hexamethylenetetramine, iodoform, isobutylbromide, methylglyoxal sodium bisulphite, monochlorohydrine, nitrosodiethylamine, oxamide, pinacol hydrate, propionamide, sulphonal, thialdine, tribromohydrine, trichloroacetylchloride, trimethylene bromide, trional, veronal.

BENZENE AND TOLUENE DERIVATIVES

Azoxybenzene	Brown

No Color Reaction.—Ortho-bromochlorobenzene, para-bromochlorobenzene, ortho-bromonitrobenzene, meta-chloronitrobenzene, ortho-chloronitrobenzene, para-chloronitrobenzene, para-chlorotoluene, ortho-dichlorobenzene, 2-5-dichloronitrobenzene, iodosobenzene, isopropylbenzene, meta-nitroboluene, ortho-nitrotoluene, para-nitrotoluene, mesitylene, styrene, para-xylenesulphonic acid.

ANILINE AND DERIVATIVES

ortho-Anisidine	Violet black, acid alone
Benzanilide	Deep violet
ortho-Benztoluide	Reddish violet
para-Bromoaniline	Reddish violet to brown
ortho-Phenetidine	Deep violet, acid alone
para-Phenetidine	Light violet, acid alone
Phenyl-beta-diphenylamine	Green, acid alone
ortho-Tolidine	Deep orange

No Color Reaction.—Acetoanilide, acetyl-para-anisidine, acetyl-ortho-methyltoluidine, acetyl-para-methyl-toluidine, acetylphenetidine, acetyl-ortho-toluidine, acetyl-para-toluidine, meta-acetxylidine, aminoazobenzene, 2-aminotoluene-4-sulphonic acid, 2-aminotoluene-5-sulphonic acid, 4-aminotoluene-2-sulphonic acid, aniline, meta-anisidine, para-anisidine, para-benztoluide, para-bromoacetanilide, meta-bromoaniline, ortho-bromo-aniline, chloramine, meta-chloroaniline, ortho-chloroaniline, para-chloroaniline, 1, 2, 4-dichloroaniline, 2, 5-dichloroaniline, 1, 2, 4-dinitroaniline, exalgine, meta-nitroaniline, para-nitroaniline, meta-nitrodimethylaniline, para-nitrodimethylaniline, nitroso-dimethylaniline, 1, 2, 3-nitrotoluidine, 1, 2, 4-nitrotoluidine, 1, 3, 4-nitrotoluidine, meta-toluidine, ortho-toluidine, para-toluidine, tribromoaniline, trinitroaniline, 1, 2, 4-xylidine, 1, 3, 4-xylidine.

PHENOLS AND DERIVATIVES

meta-Aminophenol	Dirty green
ortho-Aminophenol	Light violet, acid alone
para-Aminophenol	Blue black, acid alone
5-Benzalamino-2-cresol	Yellowish green, acid alone
para-Benzalaminophenol	Green, acid alone
Catechol	Green, acid alone
ortho-Chloromercuriphenol	Yellowish green
para-Nitrophenol	Pink
Phloroglucinol	Slate to green

No Color Reaction.—Acetyl-meta-aminophenol, acetyl-para-aminophenol, benzoylthymol, para-bromophenol, carvacrol, ortho-chlorophenol, para-chlorophenol, meta-cresol, ortho-cresol, para-cresol, 3, 5-dibromo-ortho-cresol, 2, 4-dichlorophenol, dimethylhydroresorcinol, 2, 3-dinitrophenol, 2, 4-dinitrophenol, 2, 6-dinitrophenol, meta-nitrophenol, ortho-nitrophenol, orcinol, phenol, picric acid, pyrogallic acid, tetrabromo-ortho-phenol, thymol, tribromophenol, trichlorophenol, xylenol.

AROMATIC ACIDS

Anisic acid	Brown, tinge of violet
Benzilic acid	Magenta, acid alone
Cinchophen	Light green
Cumaric acid	Red to green
Diiodosalicylic acid	Dark yellow
Diphenylacetic acid	Yellow to dark green
Mandelic acid	Brown

No Color Reaction.—Acetylsalicylic acid, meta-aminobenzoic acid, para-aminobenzoic acid, *dl*-aminophenylacetic acid, anthranilic acid, arsanilic acid, meta-bromobenzoic acid, ortho-bromobenzoic acid, para-bromobenzoic acid, meta-chlorobenzoic acid, ortho-chlorobenzoic acid, para-chlorobenzoic acid, cinnamic acid, gallic acid, 5-iodosalicylic acid, para-mercuri-chlorobenzoic acid, metanilic acid, naphthionic acid, meta-nitrobenzoic acid, ortho-nitrobenzoic acid, para-nitrobenzoic acid, quinic acid, salicylic acid, tannic acid, terephthalic acid, ortho-toluic acid, para-toluic acid.

AROMATIC ACID DERIVATIVES

Benzyl benzoate	Brown
Neocinchophen (ethyl-6-methyl-2-phenylquinoline-4-carboxylate)	Brownish green

No Color Reaction.—Benzamide, benzoic anhydride, butyl benzoate, cumarin, ethyl benzoate, ethyl salicylate, isoamyl benzoate, isoamyl salicylate, isobutyl benzoate, methyl benzoate, methyl cinnamic ester, methyl salicylate, nicotinic acid nitrate, meta-nitrobenzoyl chloride, para-nitrobenzoyl chloride, phenyl salicylate, phthalimide.

AROMATIC ALDEHYDES, ETHERS, ALCOHOLS, AND KETONES

Benzalacetophenone	Brown
ortho-Nitrobenzaldehyde	Red, acid alone
5-Nitrosalicylaldehyde	Dirty green
Salicylaldehyde methyl ether	Greenish brown, acid alone
Saligenin	Pink, acid alone
Vanillin	Brown

No Color Reaction.—Para-aminoacetophenone, anisaldehyde, anisole, benzalacetone, benzhydrol, benzophenone, ortho-bromoanisole, para-bromoanisole, ortho-bromonitrobenzaldehyde, 1, 2, 5-bromosalicylaldehyde, ortho-chlorobenzaldehyde, isophthalaldehyde, meta-methoxysalicylaldehyde, methylacetophenone, para-nitroanisole, phenetole, phthalic acid aldehyde, piperonal, salicylaldehyde, tetramethyldiaminobenzophenone, para-tolylaldehyde.

HETEROCYCLIC COMPOUNDS

Isatin	Brown
Piperidine	Brown

No Color Reaction.—Acridine, antipyrine, dimethyl-pyrone, furoic acid, 6-nitroquinoline, oxyquinoline, quinaldine, quinoline, skatole, succinimide.

HYDROAROMATIC COMPOUNDS

Carvene	Yellow-brown, acid alone

No Color Reaction.—*d*-Borneol, *l*-borneol, *dl*-camphor (natural), camphor (synthetic), camphoric acid, camphor sulphonic acid, carvenone, limonene, menthol, quercite, terpineol, terpenyl acetate.

NAPHTHALENE AND ANTHRACENE DERIVATIVES

Alizarin	Reddish violet, acid alone
Dibromoanthracene	Light brown
beta-Naphthol	Green with black streaks
Naphtholmethyl-alpha-ether	Green, acid alone
alpha-Naphthylamine	Bluish grey, acid alone
alpha-Naphthylaminoazobenzene	Deep violet, acid alone
Nitroso-beta-naphthol	Brown, acid alone

No Color Reaction.—Acenaphthene, acet-alpha-naphthalide, acet-beta-naphthalide, alpha-bromonaphthalene, 1, 5-dinitronaphthalene, beta-naphthalenesulphonic acid, naphthalic anhydride, beta-naphthylamine, alpha-naphthylisocyanate.

MISCELLANEOUS AROMATIC COMPOUNDS

Amarine	Green
Benzcatechin	Dark green
Benzoin	Green, acid alone
Benzylphenylhydrazine	Rose violet
Fluorene	Dark green
Phenanthrene	Greenish brown
Phenanthrenequinone dioxime	Reddish brown, acid alone
Phenolphthalein	Reddish orange, acid alone
meta-Phenylenediamine hydrochloride	Black, acid alone
Tetrabromophenolphthalein	Violet red, acid alone
Thymolphthalein	Magenta, acid alone
Triphenylmethane	Brown, traces of violet

No Color Reaction.—Abeitic acid, adrenaline, benzil, 2, 4-dinitrophenylhydrazine, diphenyl, isoamylphenylhydrazine, isoeugenole, ortho-nitroacet-meta-xylidide, meta-nitrobenzhydrazide, para-nitrophenylhydrazine, phenylhydrazine hydrochloride, quercite, rheumatine (saloquinine salicylate), salvarsan, thiosemicarbazide, ortho-tolunitrile, para-tolunitrile, para-tolylisothiocyanate, para-tolylquinolinesulphate, para-tolylthioquinanthrene, tumeric.

The color reactions for the tests where an equal amount of impurity was added to the strychnine were recorded, and also the reactions where five times the amount of impurity was added; but the listing of these would require too much space. Therefore, only those compounds which caused the violet color to be completely masked will be given. With the remainder of the compounds, many gave no interference, whereas others gave more or less interference.

Organic compounds which completely covered up the Otto test for strychnine when present in equal amounts were: Aesculine, meta-aminophenol, azoxybenzene, benzilic acid, benzohydrol, para-benztoluide, dionine, diphenylacetic acid, diphenylthiourea, beta-naphthol, alpha-naphthylamine, alpha-naphthylisocyanate, phenanthrenequinone dioxime, rheumatine, thymolphthalein, orthotolidine.

Organic compounds which completely covered up the Otto test when present in amounts five times that of strychnine, in addition to those listed above were: Acet-alpha-naphthalide, acet-beta-naphthalide, meta-acetxylidine, acetyl-meta-aminophenol, acetyl-para-aminophenol, acetyl-para-anisidine, amarine, aminoazobenzene, para-aminophenol, apomorphine, benzalacetophenone, 5-benzalamino-2-cresol, para-benzalaminophenol, benzophenone, berberine, brucine, orthochloromercuriphenol, colocynthin, cotarnine hydrochloride, diiodosalicylic acid, elaterin, heroine, 5-iodosalicylic acid, isoamylsalicylate, isoeuginol, morphine, beta-naphthalenesulphonic acid, naphthionic acid, naphtholmethylalpha-ether, beta-naphthylamine, neocinchophen, meta-nitrophenol, para-nitrophenol, nitroso-beta-naphthol, oenanthol, phenacaine, phenanthrene, phloridzin, phloroglucinol, piperine, salicin, sanguinarine nitrate, thiosemicarbazide, paratolylisothiocyanate, triphenylguanidine, tryrosine, veratrine.

When a study is made of the preceding data, it will be noted that there were twenty-three compounds which gave some shade of violet, lavender, or purple. Some of these were very similar to the strychnine test and might be mistaken for

it. Of these twenty-three tests, there were eleven which gave the violet, lavender, or purple color with the sulphuric acid alone. The color with the acid would account for some of the positive tests which are obtained with such reagents as Fröhde's, Mandelin's, and the dimethylaminobenzaldehyde reagent.

In general, the compounds giving a test similar to that of strychnine belong to no definite group. The alkaloids and aniline derivatives, however, gave the largest number of positive tests.

There were a few organic compounds which interfered with the test. Many of these, however, would be removed by different organic solvents in a carefully conducted analysis.

There were somewhat fewer positive tests for strychnine given by the Otto test than by the Mandelin test, but the number of substances which interfered with the former test was somewhat greater.

CONCLUSIONS

1. A large number of organic compounds have been tested with the Otto-Strychnine reaction. A number of compounds have been found which give the same test as does strychnine.

2. The interferences caused by organic compounds as impurities have been determined.

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STUDIES OF THE MECHANISM OF PAIN IN PEPTIC ULCER*

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SEVERAL theories have been advanced by various authors in an attempt to explain the mechanism of pain in peptic ulcer. These theories may be discussed under the following headings:

1. Increased muscle tension
2. Chemical irritation of the ulcer
3. The compression theory of Kinsella

1. *Muscle Tension Theories.*—Hurst in 1911[1] considered that pain in peptic ulcer was due to strong peristaltic waves advancing against a pylorus that fails to relax, "achalasia." Glaessner, Kreuzfuchs, and others thought that spasm of the pylorus and of the duodenal cap was the most important factor in ulcer pain.

Carlson, Guinzburg and associates, Hardt, and others made kymographic tracings from intragastric balloons. These tracings showed that pain was felt at the time of or just after maximum hunger contractions.

Reynolds and Mc Clure[2] observing ulcer patients fluoroscopically found various types of motor phenomena during the painful phase in patients with peptic ulcer. The motor activity varied from quiescence to intense activity.

Ortmeyer,[3] on the other hand, observed that no change occurred in the character of gastric contractions during relief of pain by alkalies.

Wilson[4] examined fluoroscopically 16 duodenal ulcer patients while in pain. He found contracted, spastic duodenal caps in all of these patients. By manual manipulation he managed to partially fill the duodenal cap in 13 of the 16 patients. Relaxation shown by filling of the cap was immediately followed by pain relief in all of the 13 cases. Wilson concluded with the hypothesis "that relief of pain is due to relaxation of musculature of the caput and conversely, that pain is due to overaction of the duodenal caput with or without abnormal local contraction or implication of the pyloric sphincter."

Apparently increased tissue tension, due to contraction of muscle or increased peristalsis, plays a rôle in the mechanism of pain in patients with peptic ulcer.

2. *The Theory of Chemical Irritation of the Ulcer.*—That pain in duodenal ulcer cases can be caused by exposing the ulcer to the action of hydrochloric acid has been shown by Bonninger.[5]

Palmer[6] showed that when a sufficient quantity of 0.5 per cent hydrochloric acid was injected into the stomach of a patient with peptic ulcer, in the active stage of the disease, typical ulcer pain was produced in 95 per cent of his cases.

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After the onset of pain, aspiration of the entire contents of the stomach resulted in immediate relief. Ingestion of alkalies sufficient to considerably reduce the acidity of stomach contents also resulted in pain relief. He further showed that as the ulcer patient became symptom-free, the pain-sensitizing action of 0.5 per cent HCl. becomes less. Palmer regards this reaction as an index of healing in ulcer.

Hurst, and Reynolds and Mc Clure failed to cause ulcer pain by injection of hydrochloric acid.

Despite this, it seems apparent that in peptic ulcer under certain conditions, the acidity of the gastric contents is a factor in the mechanism of ulcer pain.

3. *Compression of Sensory Nerves.*—Kinsella[7] in a very complete monograph criticizes previous attempts to explain the pain mechanism in ulcer as being too limited in their scope. He introduced a concept whereby ulcer pain is explained primarily by compression of sensitized sensory nerves in and around the ulcer base.

Kinsella points out that a moderate amount of compression is exerted by the edema and inflammatory exudate on the intrinsic sensory nerves around the ulcer base. Peristalsis and muscle spasm following a meal, augment this tension. Furthermore, at a specific interval after eating, the vascular channels of the antral and pyloric regions become engorged, thereby adding still another factor to increase local tension. Compression, therefore, is attained by the summation of the three factors; inflammatory edema, increased muscle tone or spasm, and localized vascular engorgement, all occurring in and around the ulcer at a specified time after meals. Kinsella concludes that ulcer pain is caused by compression of sensitized nerves around the ulcer at that time. Ulcer pain relief depends on decrease in tissue tension. Alkalies, when ingested, relax the musculature of the pylorus and duodenum. This was shown roentgenographically by Carman and by Kinsella. Food ingestion also decreases ulcer pain. As the stomach fills, the entire gastric vascular bed becomes engorged. In order to supply part of the required blood to the entire stomach, the vascular engorgement of the ulcer area necessarily diminishes. As local engorgement decreases, so also does the tissue tension in the ulcer region, and hence the compression pain is relieved.

I. INDIVIDUAL SENSITIVITY TO PAIN

Another factor is probably of prime importance in the problem. This consists in the individual susceptibility of the patient to pain.

Libman[8] pointed out in 1926 that individuals may vary widely in their sensitivity to a standard pain-producing stimulus. He stressed the problem in relation to coronary artery disease and also ulcer.

Later Crohn[9] reported that in hyposensitive individuals, peptic ulcer caused little or no pain. Hypersensitive individuals, on the contrary, definitely experience the pain caused by their ulcer. Individual sensitivity to pain seems so important a factor in interpreting symptomatology that it was decided to reinvestigate the relationship of factors associated with ulcer pain in the light of individual pain sensitivity.

The subjective symptom of pain in disease seems dependent upon the sensitiveness of the individual. Thus the phlegmatic Nordic may respond less actively to a standard painful stimulus than the hypersensitive Latin. A simple clinical test was introduced by Libman so that patients can easily be examined as to their individual pain sensitiveness. The test is performed as follows: The examiner, using the side of the ball of his thumb, makes firm pressure first on the mastoid, then on the styloid process between the tip of the mastoid and the angle of the jaw of the patient. Both sides are examined. The mastoid is the control point. The response of the patient to styloid pressure constitutes an index of pain sensitivity. A normal response is interpreted by a facial contortion indicating pain; hypersensitive patients wince, jerk the head away, and often cry out with pain; hyposensitive patients have slight or no change in their facial expression despite a strong increase in thumb pressure. In these studies patients were classified as normal; hypersensitive, 1-plus and 2-plus; hyposensitive, 1 minus and 2 minus. A significant fact in working with Libman's valuable clinical sign is that psychic manifestations or so-called "nervousness" and pain sensitivity are not directly related. That is, an individual may be insensitive to pain as determined by styloid pressure and yet be markedly psychoneurotic.

The relationship of typical peptic ulcer symptomatology to pain sensitivity of the individual as determined by Libman's sign was investigated. All patients were classified in two groups according to subjective symptoms. Patients were considered typical in symptomatology when they complained of localized epigastric pain definitely related to meals, pyrosis, night pain, possibly vomiting; these symptoms often being relieved by the ingestion of alkalies and food. The symptomatology was considered atypical if pain was vague or absent or if substitution symptoms, such as gas or heart burn or pressure alone were present. Cases were also considered atypical where the diagnosis of ulcer was made after investigation of the patient for painless hematemesis, painless vomiting, and for the vague painless dyspeptic symptoms just described. Three cases of sudden perforation with no previous gastric symptoms were included.

Material.—Ninety-nine patients with duodenal ulcer were studied and 120 clinical observations made. Sex distribution: Male 80, and female 19. Youngest twenty-one, and oldest sixty-seven years. Duration of ulcer symptoms: Shortest three weeks, and longest twenty years.

The presence of ulcer was proved roentgenographically in all cases and confirmed by operation in 12.

Observations.—In this group of 99 patients taken as a whole, sensitiveness as tested by Libman's sign was distributed as follows: Normal 28, hypersensitive 31, and hyposensitive 40. The preponderance of individuals hyposensitive to pain is possibly to be expected in this dispensary group, more exposed and accustomed as they are to rigorous conditions of life.

In eliciting the history we found that 74 (75 per cent) of our 99 patients had symptoms at some time which were typical of peptic ulcer. This group of ulcer cases with typical symptoms when examined for pain sensitivity by Lib-

TABLE I

PEPTIC ULCER SYMPTOMATOLOGY AND PAIN SENSITIVENESS. PATIENTS EXAMINED, 99

SYMPTOMS	CASES	PAIN SENSITIVENESS
Typical	74 (75%)	26 (35%) Hypersensitive 23 (31%) Normal 25 (34%) Hyposensitive
Atypical	25 (24%)	5 (20%) Hypersensitive 5 (20%) Normal 15 (60%) Hyposensitive

man's test were equally distributed in the three groups: Normal (23 per cent), hyposensitive (25 per cent), and hypersensitive (26 per cent) (Table I). Twenty-five ulcer cases with atypical symptoms had little or no pain. In these atypical cases we rather expected to find hyposensitiveness to pain according to Libman's test. Actually 15 cases (60 per cent) were hyposensitive, 5 cases (20 per cent) were hypersensitive, and 5 cases (20 per cent) were normal when tested.

II. PAIN DUE TO THE COMPRESSION FACTOR AS TESTED BY PERCUSSION TENDERNESS

During the examination of patients in the active stage of peptic ulcer, it was noted that percussion in the epigastric region revealed a localized point of tenderness. This area, in size no larger than a half dollar, was definite in its demarcation from the remaining relatively insensitive epigastrium. A tender point in the epigastrium similar to the above has been mentioned by Mac Lean, Crohn, and Bolton in writing on the physical diagnosis of ulcer. Bolton called it the "Hyperalgesic Point." To elicit percussion tenderness, fairly heavy percussion is made on the relaxed epigastrium of the supine patient. If a point of definite and sharply localized tenderness is not found, percussion is repeated after the patient has been asked to inspire and hold the breath in deep inspiration. In calling this sign "positive" it is essential to observe that the tenderness must be definite and sharply localized in area. Patients having slight, absent, or mild diffuse tenderness, are considered "negative."

The mechanism involved is not entirely clear. It is probable that in percussing, the plexor impulse is transmitted by vibration through the abdominal wall and intermediate tissues directly to the inflamed region surrounding the ulcer base. This vibratory impulse affects the inflamed nerves already under tension in the indurated tissues around the ulcer. It is also possible that the intragastric pressure and the tissue tension may be increased directly or reflexly by this maneuver. This sudden mechanical disturbance results in the production of momentary pain directly under the pleximeter finger. The use of percussion in the erect position as a diagnostic measure in ulcer has been described by Erhlich in 1923 and Kohn in 1928.

Ninety-nine patients were examined for tenderness to percussion using the technic just described. A positive reaction was found in most patients examined during the stage of ulcer activity. Patients examined in the remission or inactive, symptom-free stage of the disease were usually negative to "percussion tenderness."

The statistics are as follows:

Fifty-five (46 per cent) observations were made while the patients were in the active symptomatic stage of the disease. Forty-seven (85 per cent) of these responded positively when examined by percussion tenderness. Only 8 (15 per cent) active cases were negative to percussion. Six of these were hyposensitive when examined by Libman's test. In these individuals, possessing apparently a high threshold of pain sensitiveness, it is likely that percussion is an inadequate stimulus for eliciting pain.

Arbitrarily we considered that one week or longer of freedom from ulcer symptoms placed the patient in the remission or inactive stage of the disease. Sixty-five (54 per cent) patients were examined while symptoms were not active. Some of these had previously been examined in the active stage. Of these 65 inactive cases, 46 (71 per cent) were negative for "percussion tenderness." Despite inactivity at the time of examination, 19 (29 per cent) showed positive "percussion tenderness." Many of these had been recently active (one to four weeks previously). It is possible that the pain producing factor, which can be induced by percussion, is still active despite the absence of ulcer symptoms.

Table II shows the relationship of "percussion tenderness" to symptomatology, the Palmer Test, and pain sensitivity. Patients showing positive percussion tenderness usually had typical symptoms (88 per cent). Seventy-

TABLE II

THE RELATIONSHIP OF "PERCUSSION TENDERNESS" TO SYMPTOMATOLOGY, ACTIVITY, PAIN SENSITIVENESS AND PALMER'S ACID TEST

MATERIAL: 120 EXAMINATIONS ON 99 CASES OF PEPTIC ULCER

"PERCUSSION TENDERNESS"	SYMPTOMATOLOGY	ACTIVITY	SENSITIVENESS	ACID TEST
	Typical 57 (88%)	Active 48 (74%)	Hypersen. 23 (36%)	Pos. 20 (45%)
			Normal 21 (32%)	
Pos. 65 (55%)	Atypical 8 (12%)	Inact. 17 (26%)	Hyposens. 21 (32%)	Neg. 24 (55%)
	Typical 33 (60%)	Active 7 (13%)	Hypersen. 12 (24%)	Pos. 5 (12%)
			Normal 14 (26%)	
Neg. 55 (46%)	Atypical 22 (40%)	Inact. 48 (87%)	Hyposens. 29 (52%)	Neg. 37 (88%)

four per cent were in the active stage of the disease at the time of examination. The acid test meal was positive in 45 per cent. Sensitivity to pain in this group was equally divided into the normal, hyper-, and hyposensitive groups.

On the other hand, of the patients with negative "percussion tenderness," 87 per cent were in the inactive remission stage of the disease at the time of examination, 88 per cent were negative to the acid test and hyposensitive patients predominated over normal and hypersensitive in the ratio of 2 to 1. From this study it appears that a positive response to percussion tenderness is a valuable aid in the physical diagnosis of peptic ulcer especially in a patient with typical ulcer symptoms who is in the active stage of the disease.

III. PAIN DUE TO CHEMICAL IRRITATION PRODUCED BY HYDROCHLORIC ACID

As stated above Palmer found that hydrochloric acid produced pain in cases of peptic ulcer. Palmer's technic was carried out in 80 patients. Briefly this consisted in evacuating the contents of the fasting stomach and then instilling 200 c.c. of 0.5 per cent hydrochloric acid through the Rhefuss tube. Similar amounts of acid are instilled at half-hourly intervals for a total of 600 c.c. Pain, similar to usual ulcer pain of the individual, when produced within one and one-half hours after beginning the test indicates a positive response.

Observations.—Thirty-four patients were examined while in the active stage of the disease. Of these 21 (62 per cent) had a positive reaction, that is, typical ulcer pain was induced by the acid. Palmer reported that over 90 per cent of active cases gave a positive response to this test. Forty-six cases in

TABLE III

ACTIVITY OF ULCER SYMPTOMS AND PALMER'S ACID TEST MEAL

	ACTIVE STAGE OF ULCER	INACTIVE REMISSION STAGE
Patients Examined	34	46
Positive	21 (62%)	3 (7%)
Negative	13 (38%)	43 (93%)

TABLE IV

SENSITIVENESS TO PAIN AND PALMER'S ACID TEST MEAL IN ACTIVE ULCER CASES

	PALMER TEST		PALMER TEST
Positive	21	Negative	13
	Sensitiveness to Libman's Sign		
Normal	6	Normal	6
Hypersensitive	4	Hypersensitive	2
Hyposensitive	11	Hyposensitive	5

the remission stage were examined by the Palmer acid test. Only 3 (7 per cent) gave a positive response (Table III). The pain sensitivity of patients with positive Palmer tests was noted. No definite relationship was found in this small series (Table IV).

SUMMARY AND CONCLUSIONS

1. The rôle of muscle tension, chemical irritation, and nerve compression in the mechanism of ulcer pain is discussed.

2. The importance in the problem of individual sensitiveness to pain is stressed.

3. Studies in patients with ulcer in the active and remission stages show that (a) percussion tenderness (muscle tension and nerve compression) is present in 85 per cent of patients during the active period of the disease. This is a helpful sign in the physical diagnosis of ulcer. (b) Patients with typical ulcer history may be hypersensitive, hyposensitive, or normally sensitive to pain. (c) Patients with atypical ulcer symptomatology, however, are mostly hyposensitive to pain. (d) The Palmer Acid Test Meal (chemical irritation)

is positive in the majority of ulcer patients during the active stage and negative in the remission stage.

I wish to express my thanks to Dr. Asher Winkelstein, Chief of the Gastro-Intestinal Clinic of the Mount Sinai Hospital, for his suggestions and advice, and to Mrs. Beatrice Weil for her technical assistance.

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FOOD ALLERGY AS A COMMON PROBLEM*

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THERE are two general types of food allergics, the fortunate and the unfortunate. The former comprise those who were lucky enough to become sensitive to foods which are eaten only intermittently or occasionally. They have no difficulty in attributing their untoward symptoms to the correct cause. Instinctively they thereafter avoid the offending foods and are relieved of their allergic manifestations. As we shall see this forms a large group and these "fortunate allergics" are usually considered nonallergic.[1]

The second or unfortunate group suffer the misfortune of becoming sensitive to staple foods, foods eaten frequently, usually daily. Chronic exposure, resulting in more gradual evolution of symptoms, a realization that in the past all of these foods have been eaten with impunity, and an understanding that they are not naturally poisonous, all combine to keep the sufferer ignorant of the cause of his symptoms. The man who experiences an explosive outbreak of urticaria with the advent of each strawberry season finds no difficulty in discovering its etiology. Thereafter he avoids strawberries. His friend, with subacute or chronic symptoms and sensitive to wheat is less likely to spontaneously discover the source of his trouble.

The allergic group representing from 7 to 10 per cent of the entire population is recruited chiefly from the unfortunates.[2] The fortunates are usually considered as in the nonallergic group because they have at some time in the

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past solved their own problem and at the time of questioning they have no allergic symptoms. I use the terms fortunate and unfortunate, since so far as we know at present it is to a great extent just an element of chance to what one will become sensitive.

Other terms might be equally appropriate, as minor allergy and major allergy; or acute and subacute or chronic; or simple and complex. Each of these classifications is open to some criticism. It is sufficient that we understand that in the minor or fortunate group we are dealing with transient or passing episodes while in the major or unfortunate group we are faced with the problem of an established malady.

MINOR ALLERGY AND TRANSIENT ALLERGY

I have felt that we should be able to reach a clearer understanding of food allergy were we to direct more attention to an understanding of the simple or transient episodic manifestations of the phenomenon. With this in mind I have made a study of a number of so-called nonallergics, searching for evidences of allergic reactions in the past. Analysis of only the first 100 questionnaires has been completed and while the series is not sufficiently large to justify final conclusions, the observations are most interesting. Among the 100 so-called nonallergics, we found histories of former acute allergic manifestations in 61 per cent. In an additional 11 per cent the story was suggestive but not definite. The remainder were negative. If to the 61 per cent we add the 7 to 10 per cent of frank allergics, we may infer from this series that upward of 70 per cent or more are allergic at one time or another. Of the 61 per cent, 46 gave positive histories for food allergy and almost without exception they could name the foods causing symptoms.

A comparison of the foods recognized by the patient as causing minor allergy with those found by testing to be responsible for major allergy is of interest (Table I). With the major allergics, I have found by skin tests[3] that the following foods are chief offenders, in order of frequency; wheat, milk, bean, egg, and Irish potato. The minor allergics, on the other hand, name the following foods in order of frequency as chief offenders; cucumber, watermelon, strawberry, tomato, onion, and cabbage. In this group wheat does not appear at all, egg and milk only once, potato and bean only twice each. Most of the remaining foods are such as are eaten occasionally

I find evidence in my studies that the normal physiologic tendency is toward a gradual loss of specific sensitizations. There has in the past been a rather general impression that once one becomes sensitized this specific sensitization tends to persist throughout life. But students of allergy have in the last few years had the opportunity of watching sensitizations appear and disappear, to be replaced by new ones. Likewise, serial retesting will show that foods and other allergens, once positive, sometimes become negative, while others formerly negative become positive. It is but a simple step farther to postulate that the natural tendency of specific sensitization is to a gradual disappearance. The rapidity of this disappearance depends of course upon the degree or intensity of the sensitization and also upon whether the reaction

is kept active by repeated or continued contact with the sensitizing allergen. If avoidance of contact could be carried out sufficiently long with every allergen, the probability is that our sensitizations would eventually disappear. New ones of course may take their places. Allergists for example have almost universally concluded that food allergy is better handled through the method of avoidance than with attempts at desensitization either orally or parenterally. Prolonged contact intensifies the allergic reaction and delays recovery. I refer here more particularly to food allergy. Perennial pollen desensitization is an apparent exception which, however, I believe that we can reconcile to the hypothesis.

As examples of transient allergy the following may be cited:

Mr. V. in the summer of 1929 experienced attacks of colitis with cramping pains and diarrhea each time that he ate peaches. Almonds which belong to the same biologic group as the peach caused the same reaction. One year previously he had experienced typical vasomotor rhinitis each time following the drinking of rye whisky. None of these three ingestants produced symptoms prior to or subsequent to these years.

Mr. H. experienced hives after eating tomatoes during the World War and for two years thereafter. Since then he has been able to eat them without reaction, usually eating them about twice daily.

Miss R., aged fifteen, had had hives at age ten for a period of two months attributed to strawberries. She avoided them for a time but can eat them now without difficulty.

Mr. R. experienced urticaria from strawberries in childhood. He eats them now without discomfort.

Mrs. B. found that during one summer watermelon consistently produced vomiting and diarrhea, but since then, she has had no trouble.

Mrs. F. eight years ago found that watermelon produced angioneurotic edema of the hands and tongue. Even the juice of watermelon on the hands produced swelling. Watermelon now causes no symptoms.

Miss W. observed that several years ago strawberries caused abdominal cramps and nausea. She avoided them for several years and this year has taken them without discomfort.

Mrs. M. three years ago had hives in the summer time, cause unexplained. Since then she has had no return.

Mrs. C. experienced eczema in childhood involving the hands only and lasting for three months. This was presumably due to chocolate. She has had no return of trouble until within the last few months when the eating of chocolate produces urticaria and cardiac palpitation, often with headaches. Plums consistently produced diarrhea a year ago: none before or since.

Mrs. B. experienced diarrhea from cut corn in childhood. She eats corn without difficulty now.

Mr. G. several years ago regularly had sour stomach and heartburn from the eating of cucumbers. He now eats them without difficulty.

The transient allergic rarely needs advice or study by the physician. He himself realizes the etiology of his symptoms and cures himself by avoidance. Not all lose their sensitization after a period of avoidance. Not a few report the reappearance of symptoms each time they eat the offending food. This group obtains relief by one of three methods, (a) outgrowing the specific sensitization, (b) continued avoidance, and (c) unconscious incidental changes in their routine by which they unwittingly are removed from the causative

agent. This happens more frequently in inhalant and contact allergy than in food allergy. A lady in her forties had had asthma in childhood which, as she stated, she outgrew. She was sensitive to cat hair and remarked that while they had had cats in the house in childhood she had always despised them and that she had had none for years. She had relieved herself intuitively by avoidance.

MAJOR OR FRANK ALLERGY

The physician is, however, more frequently faced with the problem of determining the offending food in the major or frank allergic.

Here several procedures may be followed. Realizing that the frank allergic is more likely to be sensitive to the foods usually eaten, the staples, the doctor may place his patient on an elimination diet or trial diet from which the common offenders have been deleted.[4] This would work well were it not that in addition to the staples the chronic allergic is also usually sensitive to one or more of the infrequent offenders, as is the minor allergic. Since these usually show up positive on skin testing, indeed more frequently than do the staple offenders, we find it more logical and more frequently successful to perform preliminary skin testing on the basis of which infrequent and frequent offenders may be promptly eliminated without guesswork. It is quite true that one may be sensitive to an allergen which fails to produce positive skin reaction just as one may show positive skin reaction to an allergen which fails to cause trouble. But in the great majority there is a correlation between positive skin reaction and symptoms. It has been conservatively estimated that skin testing will give only 50 per cent of reliable information on allergenic foods.[5] But if this procedure diminishes the amount of necessary subsequent work by 50 per cent it is well worth employing and is indeed the foundation procedure for subsequent investigative superstructure.

TESTING METHODS

Sensitization tests may be performed either by the scratch or cutaneous method or by intracutaneous or endermal testing or by passive transfer. The last is only occasionally required, particularly in the study of infants or individuals with such generalized dermatitis that there is not sufficient space for skin testing or in those with a general urticarial tendency in which all tests show up positive. In this event blood is obtained from the patient, the serum is diluted and filtered through porcelain and introduced intracutaneously into the skin of the nonallergic recipient. Later, the recipient is tested in the passively sensitized sites by the intracutaneous method, with control tests applied to areas of his nonsensitized skin.

The customary procedure in the majority of cases, however, is the scratch test and the intracutaneous test. Both have their advantages. The former possesses the advantage of safety with the disadvantage of diminished accuracy. The latter is more sensitive but occasionally dangerous because of its extreme sensitiveness. Both methods should be combined. If one would avoid the rare anaphylactic reaction, one will never do intracutaneous tests without preliminary scratch test. This is our routine procedure. As far as foods are

concerned, scratch tests are first applied with the individual foods. The positive scratch foods are removed from the intracutaneous test boards and the remainder of the series is then repeated with endermal tests. In order to reduce the requisite number of intracutaneous tests, group intracutaneous reactions are obtained, using solutions containing two or more allergens grouped together in accordance with their genetic or biologic relationships.[6]

Where intracutaneous tests are done without preliminary scratch testing, the potentialities for untoward reactions are so great that one must use very dilute intracutaneous solutions. In this case 1/5,000 concentration is usually selected. The intracutaneous test is about 100 times more sensitive than the scratch.[7] In our own work I use a scratch concentration of 1/50. If in our intracutaneous work we were to use 1/5,000 concentration or 100 times dilution over our scratch reaction, we would find that the intracutaneous test is no more sensitive than the scratch. This is the advantage of preliminary scratch testing. If the scratch reaction has been negative, one can proceed intracutaneously with a solution at least ten times more sensitive. This implies a 1/500 instead of 1/5,000 concentration. As a matter of fact we have no hesitancy in our own work in using 1/250, provided the preliminary scratch test was negative.

In short, if one is using 1/5,000 concentration for intracutaneous testing, this is no more accurate than the scratch method. But if one will use a more concentrated intracutaneous solution after preliminary scratch testing, results will be more accurate due to the finding of an additional number of low grade positive reactions. Intracutaneous extracts in which foods are grouped in accordance with biologic relationships diminish the requisite number of needlings. It is not safe to employ groups in scratch testing since each additional food in the group increases the likelihood of false negative reactions.

As a rule the intracutaneous test will show as positive some of the reactions that were negative by the cutaneous test. However, not infrequently foods and other allergens will show up positive by the scratch method, being at the same time negative intracutaneously. This is another reason why the combination of the two methods promotes greater accuracy.

Assuming that we are dealing with a case of food allergy and that the sensitization studies have shown positive reactions, we will proceed to place the patient on a special diet from which the positive reactors have been eliminated and to which adequate substitutes have been added to provide the requisite food values.

TRIAL DIETS AND THE FOOD DIARY

If, in a food allergic the program fails of results, the next logical step is the trial or the elimination diet.

The diets that have been proposed in the literature are based on the principle that in major allergy foods more frequently eaten are the more frequent offenders, and that these are especially likely to give false negative reactions on skin testing. If one will pay attention to the borderline reaction and the delayed positive, the latter assumption will not be found to be true as often

as is generally believed. But the first assumption is quite valid. Series of alternative elimination diets have therefore been proposed which provide for the elimination of the common ingestants but which do not take into consideration the undoubted fact that the major allergic is usually sensitive to one or more relatively infrequent foods as well as to one or more common foods. And several of the infrequent foods appear on the elimination diets. For this reason I object to the use of the elimination diets without preliminary skin testing. Instead, I prefer my trial diet,[3] which, however, must be individualized for each patient. It has a double basis, the elimination of staple foods and, in addition, the avoidance of those foods to which the patient was found on trial to be sensitive. It is built up on a foundation list of foods to which in my experience both groups of patients are infrequently sensitive and to which are added other foods to which the patient has been found by testing to be nonsensitive. Naturally, if the patient has been found sensitive to a member of the foundation list that also is deleted.

There are a few food allergics in whom the offending food cannot even be found after a combination of the sensitization studies and the trial diet. In this case the food diary becomes requisite. It is only of value where the symptoms are intermittent and I have found from experience that it is much more easily followed if the patient is already on a restricted diet such as the trial diet. A list is kept, daily, of all foods eaten as well as of any occurrences out of the usual routine of the day. Days on which symptoms are manifested are checked and a comparison of these checked days with the foods eaten on that day and the preceding day and with the events of these two days occasionally enables one to determine the etiologic factor.

Thus we see that the treatment of the food allergic goes along in a logical sequence based first upon the sensitization reactions, modified as need be by the trial diet, and finally checked, if necessary, with the food diary.

DISCUSSION WITH THE PATIENT

I have omitted discussion of the first and one of the most important procedures of the examination, discussion with the patient. Note that I do not state "taking the history." Discussion with the patient in allergy involves much more than routine history taking. It is because it should follow as well as precede the allergic examination that I discuss it now. Much information can often be obtained from discussion with the patient of his past allergic history prior to the institution of testing, but a surprising amount of additional information is often acquired from a continuation of the discussion after the patient has been made acquainted with the list of positive reactions. This will refresh his memory on many hitherto unremembered incidents of his past experience and will show a surprisingly increased correlation between the positive skin tests and the patient's own experiences. Discussion should include a careful inventory of the family allergic history including not only asthma, hay fever and urticaria but also eczema, sick headaches and food upsets. The same series of maladies should be investigated in the patient. Also symptoms suggestive of allergic indigestion or colitis. One should bear in mind that

the manifestations of allergy are often obscure and bizarre, and one should be on the watch for unusual symptoms which can be fitted into the picture, both at the time of the preliminary questioning and at the final discussion as well as at subsequent follow-up discussions that may be had from time to time. The following cases represent some of the unusual manifestations of food allergy.

A young lady of twenty-four complained of lack of energy. If she stays up as late as 11 o'clock she feels dead the next day. She says she could sleep indefinitely. However, at night she does not sleep soundly. She had had nocturia since childhood. She had had her appendix removed six years previously in an effort to relieve her symptoms and for two months prior to examination she had been fed increasing doses of thyroid. Her metabolic rate had been minus 16 and the asthenia has been ascribed to thyroid deficiency. However, the thyroid intake had been increased to 12 gr. daily with no improvement but with symptoms of thyrotoxicosis, daily diarrhea, trembling, palpitation, nervousness and vertigo.

Discussion with the patient brought out that each year she had a spell of urticaria which she believes is due to strawberries and tomato, that her sister develops a vasomotor rhinitis when near cats, and that her brother sneezes many times each morning when he arises. She gave only borderline reactions to the legumes, chocolate, wheat, banana, and ginger. All medication including thyroid, was discontinued. The foods mentioned were eliminated. Five days later she reported that she had more pep than she had had for months, and now, five months later, she still reports herself full of energy, free from nocturia, sleeping well and relieved of a neuritis that had been bothering her for several months.

Note that she complained of no allergic symptoms. They were brought out only after discussion. The following cases also bring out this point.

A man of thirty-five, complained of a low grade dermatitis of three years' duration, worse in the autumn, of heartburn and constipation, and of easy fatiguability. As he said, he awakened tired in the morning and had to drag himself out of bed. He was seeking relief for his indigestion. Discussion with him developed that he had had seasonal hay fever in childhood from age eight to twenty-one and occasional headaches of undetermined origin in childhood. In former years before the development of the chronic heartburn, he had had intermittent attacks of heartburn brought on definitely by cucumber, tomato, and strawberry. He was found sensitive to 14 foods including milk, peas and beans among the staples and apple, pear, peanuts, celery, cantaloupe, cucumber, berries, chocolate, tomato and banana among the occasionals. On dietary restrictions his skin rash, lack of energy and indigestion disappeared, and although he had been obstinately constipated for years, his bowels became regular. Two years later he reported that except for one interval when he had strayed from his diet he remained entirely well.

Miss M., complained of extreme dysmenorrhea and some low grade indefinite indigestion. It was found that she sneezed a great deal. Her hay fever was not sufficiently severe to justify treatment. She knew the cause to be dust. No cause other than a possible allergy was found for her indigestion.

TABLE I*

SURVEY OF ALLERGENIC FOODS

	POSITIVE REACTORS IN MAJOR ALLERGY PER CENT	FOODS BLAMED IN MINOR ALLERGY	FOOD DISLIKES
Vegetable Foods:			
Wheat	24.0	0	
Rye	3.5	0	
Barley	3.5	0	
Oat	4.5	0	
Rice	2.5	0	
Corn	4.0	2	
Cocoanut	5.5	0	
Pineapple	1.5	2	1
Onion	6.5	9	5
Asparagus	5.5	1	1
Banana	4.5	2	2
Ginger	2.0	0	
Fig			1
Buckwheat	2.0	0	
Rhubarb			4
Walnut	3.0	1	
Pecan	0	0	
Spinach	5.5	2	17
Beet	0	0	
Swiss chard	2.0	0	
Turnip	4.0	3	13
Cabbage	5.0	8	11
Sauerkraut			1
Cauliflower	3.0	0	4
Mustard	5.5	0	1
Radish	2.0	0	
Raspberry	3.0	0	1
Strawberry	0.1	10	2
Apple	3.5	2	2
Pear	3.0	0	
Almond	4.5	1	
Prune	7.0	1	
Cherry	7.5	1	
Apricot	5.5	0	
Peach	5.0	2	1
Pea	3.0	1	1
Kidney bean	12.0	2	2
Peanut	2.5	2	
Blackeye pea	4.0	0	3
Lima bean	6.0	0	
Bean (string)	3.5	0	
Lentil	4.0	0	
Lemon	2.5	0	
Grapefruit	3.0	1	2
Orange	5.0	0	
Grape	3.5	0	
Cotton seed	6.0	0	
Okra	2.0	0	9
Cocoa	4.0	4	
Tea	0.6	0	
Celery	8.0	0	
Carrot	3.0	0	10
Parsnip	4.0	0	
Parsley	0	0	
Huckleberry		1	
Olive			4
Sweet potato	1.5	1	1
Tomato	7.0	10	3
Pepper	0.6	3	3
Potato	9.5	0	

*The order in which the vegetable foods appear follows the botanical or genetic classification.

TABLE I*—CONT'D

	POSITIVE REACTORS IN MAJOR ALLERGY PER CENT	FOODS BLAMED IN MINOR ALLERGY	FOOD DISLIKES
Vegetable Foods:			
Eggplant	7.0	0	3
Coffee	7.0	0	
Pumpkin	0	1	
Squash	3.5	1	8
Cantaloupe	5.0	7	
Pickles			1
Cucumber	2.5	13	5
Watermelon	0	13	
Lettuce	3.5	0	
Animal Foods:			
Beef	2.0	0	
Veal	2.0	1	
Milk	14.0	1	
Buttermilk			1
Butter			1
Cheese		1	1
Egg	9.5	1	1
Chicken	3.4	0	1
Pork	1.0	2	
Lamb	3.0	0	8
Sea Foods:			
Clam		1	2
Shrimp		1	
Oyster			
Crab			
Lobster		1	
Fish		2	4
Herring		1	1
Sardine		1	
Caviar			1
Anchovies			2
Miscellaneous:			
Whisky		1	
Sweets		3	1
Acids		2	
Meats		3	
Condiments		1	
Mayonnaise		1	
Fruits		1	2
Brains		0	5
Tongue		0	2

*The order in which the vegetable foods appear follows the botanical or genetic classification.

Her chief complaint was dysmenorrhea which she described as intense cramps with sometimes, fainting spells on the first and third days.

She was found sensitive to wheat, cotton seed, corn, and some incidental foods and was advised to avoid these during the week prior to, and through the duration of her period. She did this with relief of pain.

Miss H., also subject to ragweed hay fever, suffered from headache over the left eye, only during the catamenia. She was also found sensitive to certain foods and discovered that by avoiding them during the week prior to and through the catamenia she was relieved of these headaches.

FOOD DISLIKES

It has been suggested that a history of food dislikes suggests a sensitization to the undesired food, that dislike for a food to which the patient is unknowingly sensitive constitutes a protective reaction.[8] My own experience has been rather the reverse, that most allergics will say that they are very fond of the particular food which is responsible for their symptoms. Only occasionally have I found evidence of a correlation between dislike and sensitization.

In my series of 100 so-called nonallergics, 46 showed evidence of food allergy and 66 expressed food dislikes. Most complained of the taste, some of the appearance, and some explained that they continued to taste them for many hours after eating. The list of foods disliked is altogether different from that of foods causing minor allergic manifestations, and includes, in order of frequency, spinach, turnip, cabbage, carrot, okra, lamb and squash, with a scattering of others (Table I).

Food dislikes as well as food disagreements were usually multiple. In no instance was there entire agreement between foods disliked and foods responsible for symptoms. In four instances one among several foods and in five instances two among several foods corresponded in both groups. We may conclude, therefore, that while dislikes may occasionally be indicative they cannot be relied upon.

There is an old superstition or better tradition that certain combinations of foods which are individually harmless become harmful to certain individuals in an allergic way. This tradition crops out in my series. Whether it is an actual synergism or merely a coincidence remains for future investigation to determine. Combinations mentioned are such as milk and fruit, orange juice and ice cream, cake and cabbage, fish and milk, deviled crab and ice cream. Each of these foods eaten separately caused no reaction nor did the individual constituents of the following special dishes to which symptoms were attributed: crab flake salad, frozen fruit salad, potato salad. In these salads the cotton seed oil presumably present in the salad dressing may have been the responsible factor.

CONCLUSION

I trust that in discussing these many ramifications of the problem of food allergy I have not made it appear discouragingly complex. It is a complex problem which can only be made simple by an adequate understanding of it. The points which I have discussed should enable one to avoid most of the many pitfalls. Too many doctors and patients alike feel that the skin test is the last court and conclude if the results of skin testing fail to relieve, that allergy is not a factor.

I would emphasize particularly the need for frequent follow-ups, particularly in those who are not doing as well as one thinks they might. It is surprising how often new factors are found to crop up. The variability in sensitization from time to time and the factor of interaction with nonspecific causes are chiefly responsible for this. One should bear in mind at all times that the

allergic state is never static. It is intimately bound up with the problem of nutrition and indeed with the biochemical activities of the process of life itself. Representing as it does changing responses to a changing environment it is not at all surprising that supervision must often be continued over a prolonged period before all factors are finally brought under adequate control.

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808 Professional Building

THE INACTIVATION OF GROWTH HORMONE*

As a Result of Inadequate Refrigeration

H. S. Rubinstein, M.D., Baltimore, Md.

IN CARRYING out experiments dealing with the brain weight-body weight ratio[1] it became necessary to use anterior pituitary extracts as growth stimulators. In the course of this work it was found that while fresh extracts possessed this quality, the effect was lost when refrigeration was inadequate. It is the purpose of this communication to report on the inactivation of growth hormone as experienced in this laboratory. An extract of the anterior lobe of the pituitary gland was prepared by a modification of the Putnam, Teel and Benedict[2] technic so that 2 c.c. of the final product represented one gram of the fresh anterior lobe. Such extract when used *fresh* showed a definite growth-stimulating effect.[1] When ready for use as fresh extract this preparation was distinctly alkaline to phenolphthalein and possessed a P_H of 8.3.

Twenty-one adult female white rats (Mus norvegicus albinus) were used in these experiments and these were arranged so that only litter mates were used as controls. Litters were used which contained four or five females of which two received growth hormone, one received no injections, and the remaining one or two, injections of meat extract.

*From the Neuro-Anatomical Laboratory, Department of Anatomy, University of Maryland, School of Medicine.
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Upon intraperitoneal administration of this extract in the dosage of 2 c.c. daily (except Sunday) growth effects became quite noticeable. The controls injected with meat extract and those uninjected failed to increase in size.

It was found, however, that after a growth increase for two or three weeks the rats injected with the same preparation began to lose weight. A fresh extract, alkaline in reaction, was substituted and the next week the animals again gained weight. This weight increase and subsequent weight loss was noted repeatedly showing that the growth-stimulating effect of the extract used was lost after two or three weeks (Chart I).

A study of the inactivated extract revealed that its alkalinity had decreased to such an extent that it was no longer alkaline to phenolphthalein.

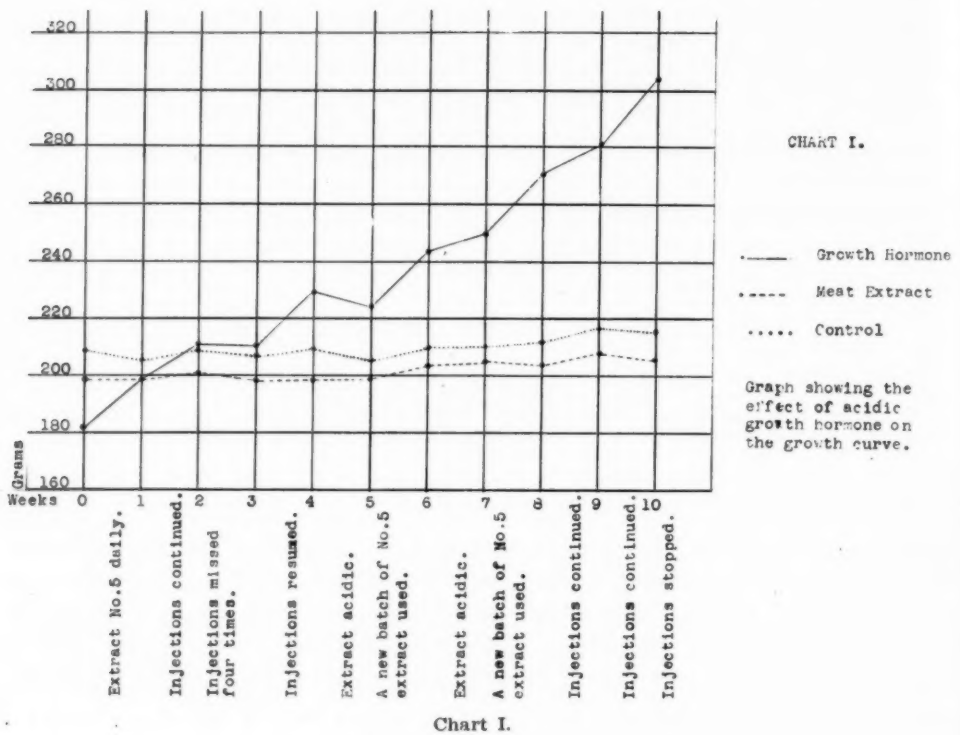

Chart I.

One of the animal groups which had reacted alternately by growth increase and weight loss was then subdivided into two. To one of these the acidified extract was continued; to the other, a fresh alkaline preparation was administered (Chart II).

It was noted that the animal receiving fresh extract again gained weight while the animal which was continued on acidified extract failed to show any gain. Some of the animals receiving acidified extract actually lost weight after a previous increase had been noted (Charts I and II). It was also found that the addition of sufficient alkali to restore the original P_H after acidity had occurred failed to restore the potency of the extract. This failure was to be expected, since if addition of alkali to acidified extract could restore

potency, the buffers of the blood should be sufficient to produce this alkalinity and growth would be obtained even after acidity had occurred.

In order to prevent the use of inactivated (acidic to phenolphthalein) extract, it was found advantageous to add an indicator to the growth hormone preparation. Accordingly, two drops of a 1 per cent alcoholic phenolphthalein solution were added to each 30 c.c. of the pituitary extract and preparations were used only as long as they retained a pinkish tinge.

Where an extract is made and immediately placed on ice, its potency lasts for several months, but where refrigeration is imperfect as in those instances where the extract has to be shipped it appears that an indicator is of value.

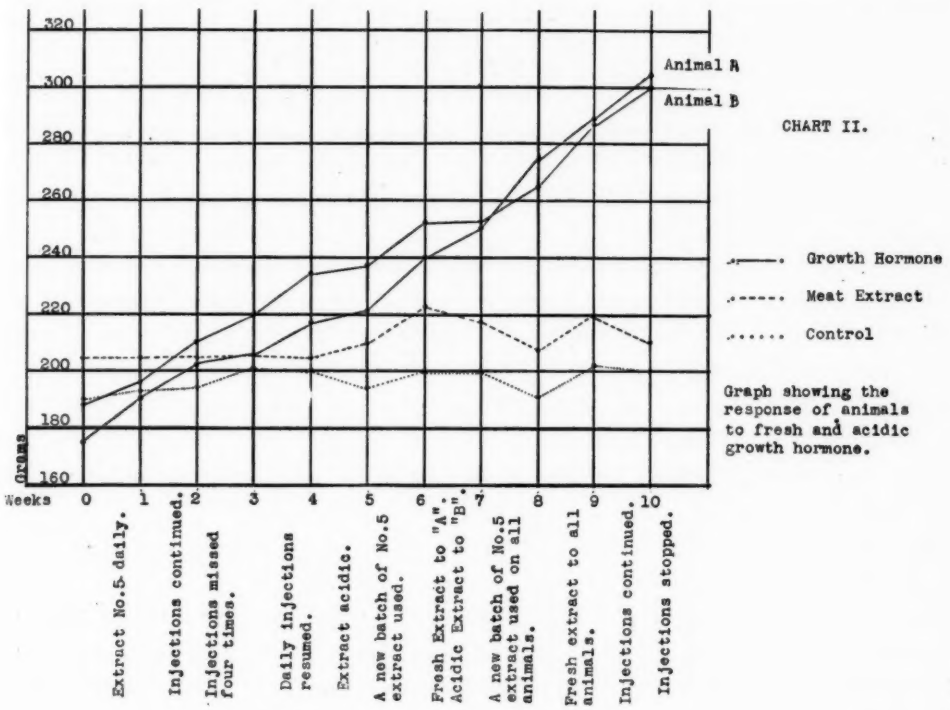

Chart II.

SUMMARY

1. Alkaline extracts of the anterior pituitary gland become less alkaline as a result of imperfect refrigeration.

2. This decreased alkalinity inactivates the growth hormone.

3. Adequate refrigeration decreases the rapidity of inactivation.

4. The adjustment of P_H after inactivation, fails to restore the potency of the extract.

5. Phenolphthalein added as an indicator serves as an index to the alkalinity of the preparation which must be maintained if the extract is to remain potent.

The author is greatly indebted to Dr. Carl L. Davis, head of this Department, at whose suggestion this paper was written.

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THE TREATMENT OF BRONCHOPULMONARY SUPPURATION OF FUSOSPIROCHETAL ETIOLOGY WITH SMALL DOSES OF NEOSALVARSAN*†

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FUSOSPIROCHETOSIS is gradually gaining recognition as an important factor in bronchopulmonary pathology. Receiving its first clinical recognition in Ceylon, India, in 1906, by Castellani,[1] who described it under the name of "bronchopulmonary spirochetosis," it has, through its cosmopolitan character, gained the attention of clinicians the world over.

It is with the hope of stimulating further study in regard to treatment of this deserving subject, that an attempt is made to relate the experiences gained from a study of 25 cases of acute and chronic bronchopulmonary suppuration in whose sputum, spirochetes, fusiform bacilli, vibrios, and other anaerobic organisms were repeatedly found.

To begin with, it should be stated that about 80 per cent of normal mouths and practically all pyorrheic mouths harbor anaerobic organisms, particularly spirochetes. These organisms are found about the teeth, tonsils, and adenoids, as pointed out by Davis and Pilot,[2] Carpenter,[3] and others.

That the buccal anaerobes may produce serious diseases was called to our attention by Plaut[4] in 1894 and Vincent[5] in 1896 when they pointed out the relationship of these organisms to Vincent's angina. That aspiration of oral contents into the lungs can easily take place has been demonstrated in animal experiments by Kline,[6] Smith,[7] Crowe and Scarff,[8] Allen,[9] Hedblom, Joannides and Rosenthal,[10] Harkavy,[11] Schlueter and Weidlein,[12] Bethune,[13] and clinically, by Myerson,[14] Daily and Daily,[15] Iglauer,[16] and Ochsner.[17]

There has been considerable discussion as to whether or not the aspirated mouth organisms are merely saprophytic contaminants of the tracheobronchial tree or actual pathogens. There is a growing belief that a previous pyogenic infection may prepare the way for the action of the anaerobes in symbiosis and contribute to the pathogenicity of the lesion.

Predisposing factors of bronchopulmonary spirochetosis are poor hygiene of mouth, such as pyorrhea alveolaris, carious teeth, infected tonsils and ade-

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noids, infected sinuses, and Vincent's angina. Operations on the upper respiratory tract or operations in general under deep anesthesia may predispose to the development of the condition. General debilitating diseases such as diabetes, pulmonary tuberculosis and cancer may be associated with the condition. The existence of previous bronchopulmonary pathology such as chronic bronchitis and emphysema, bronchiectasis, and chronic fibrosis of the lungs in general, may predispose to the development of bronchopulmonary spirochetosis.

TREATMENT

From the preceding discussion it is evident that mouth hygiene is one of the indispensable measures in the prophylactic control of this condition. Carpenter[3] states that patients without teeth and tonsils only occasionally harbor spirilla, and suggests the thought that to eradicate fusospirochetal diseases from the human race, we must remove all teeth, tonsils, and adenoids.

A review of the literature reveals the following general procedures available for the treatment of acute and chronic suppuration of the lung: (a) Prolonged bed rest, (b) bronchoscopy, (c) pneumothorax, (d) oleothorax, (e) phrenioectomy, (f) incision and drainage, (g) thoracoplasty (partial or complete), (h) lobectomy and cautery pneumectomy, (i) heliotherapy, (j) transfusions, (k) vaccine therapy, and (l) medicinal measures.

A study of the literature reveals that many drugs have been recommended for the treatment of this condition, such as tartar emetic, iodine, antimony, emetine, bismuth, and the various arsenicals such as sulpharsphenamine, salvarsan, and neosalvarsan. Vincent[18] also reported the use of a serum for the treatment of gangrene.

It is the purpose of this paper to limit the discussion to the value of the arsenicals in general and neoarsphenamine in particular in the treatment of suppuration of the lungs of fusospirochetal origin.

It is amazing to find that until very recently most writers actually failed to mention the arsenicals in their discussion of treatment of suppuration of the lungs.

Due to the accumulation of evidence strongly pointing to the potential pathogenicity of the mouth organisms, and due to the possibility that the various forms of acute and chronic suppuration of the lungs may merely represent different phases of the disease fusospirochetosis,[19] more attention is being given to the drug. Some physicians believe in its specificity, others fail to see any value in its use. On the one hand, we find Kline and Berger[20] who state, "Arsphenamine therapy is apparently as specific in this as in other spirochetal infections." On the other hand there is Miller[21] who states, "Specific therapy, particularly arsphenamine, is by no means regularly successful. In fact, in my experience, it rarely has proved to be of real specific value."

Why these opposing views, is a question that immediately confronts one and tempts one to speculate for a possible answer. It is interesting to note in this connection that to date one fails to find in the available literature any scientific discussion of dosages, frequency of administration, and reasons for favorable or unfavorable results in the treatment of suppuration with arseni-

cals. Some writers merely mention the drug without qualifying the dose; others content themselves with the statement that the dosages used are the same as in syphilis; while still others advocate intensive doses such as 0.6 to 0.9 of a gram of neosalvarsan.[20]

The value of large doses of arsenicals in the treatment of suppuration was first questioned by me[22] about three years ago when neosalvarsan was used by me in two cases of abscesses complicated by gangrene. The initial dose used in each patient was 0.3 gm. In each instance unfavorable reactions followed the administration of the drug; the temperature rose to a higher level, dyspnea was more marked, and the sputum became more foul. Both patients gradually became worse and died within a few days. The opportunity to investigate the possible value of small doses of neosalvarsan in the treatment of this condition did not present itself until October, 1930,

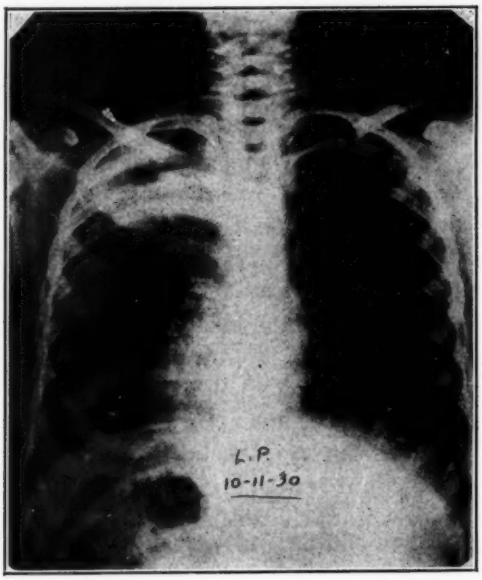

Fig. 1.

when three of the patients with acute suppuration of the lungs failed to show improvement, and were definitely worse after a reasonable time of treatment with conservative measures. However, before instituting radical treatment which seemed almost compelling, it was decided as a last conservative measure, to use neosalvarsan in small doses.

To evaluate properly the results obtained with this drug in small doses curtailed case histories of the three patients will be helpful.

CASE 1.—L. P., white boy, thirteen years of age, admitted to St. Mary's Infirmary (a part of St. Louis University group of hospitals) on Sept. 29, 1930, six days following the removal of his tonsils and adenoids under general anesthesia. On September 27 he had a sudden severe pain in left chest region, followed by fever, cough, and vomiting. On the day of admittance, the sputum became slightly foul. The white count was 8200, red count, 4,525,000, and hemoglobin 90 per cent. The temperature was 103°, pulse 120, and respirations 28. Sputum was negative for T.B., positive for elastic tissue, and sputum culture re-

vealed pneumococci, streptococci, *Micrococcus catarrhalis*, and a gram-negative rod. There was a marked shift to the left with the Arneth Schilling method.[23] The blood sedimentation rate[24] was rapid and the Wassermann was negative. Physical examination revealed dullness and diminution of breath sounds and inconstant posttussive clicks in region of left apex. A diagnosis of lung abscess was made which was confirmed by a roentgenogram (Fig. 1).

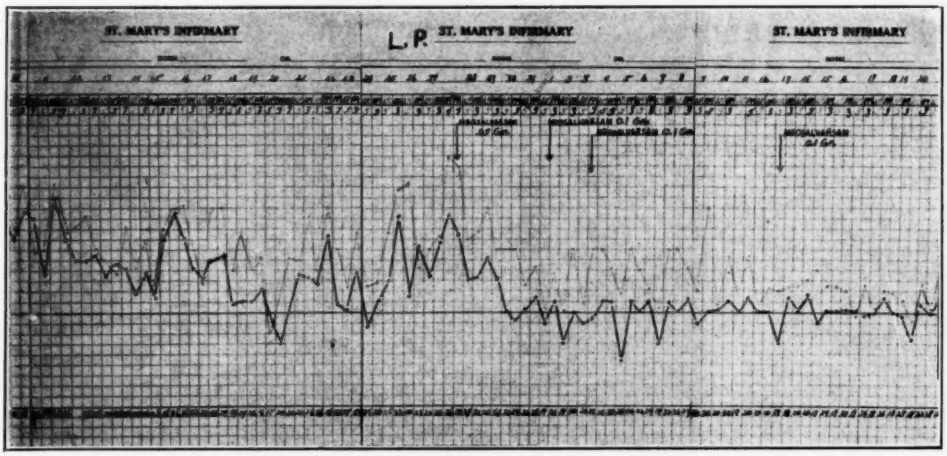

Fig. 2.

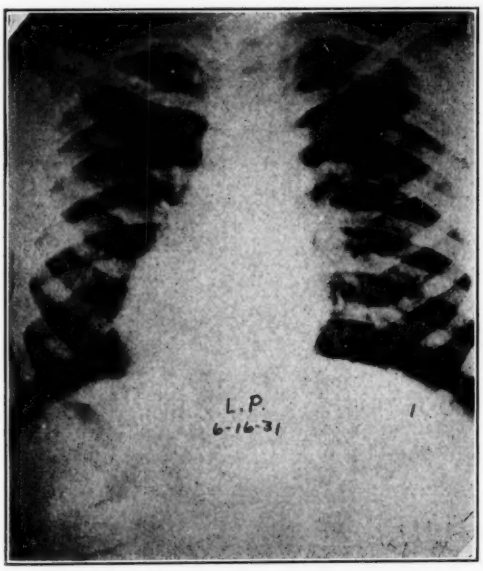

Fig. 3.

The patient was treated conservatively with bed rest, postural drainage, and symptomatic treatment. However, in spite of this treatment he became definitely worse. On the twelfth day after admittance, the sputum assumed a grayish greenish appearance, became definitely bloody, and very offensive in character. The temperature at this time was 104°, pulse 146, and respirations 48, and the white count rose from 20,100 on the twelfth of October to 33,800 on the sixteenth of October. At this time the patient was also having a hemorrhage. A diagnosis of beginning gangrene was made. On the twenty-seventh of October a dark-field examination of the sputum revealed numerous spirochetes. On the twenty-eighth of

October, four weeks after admittance, he was given 0.05 of a gram of neosalvarsan intravenously, and twenty-four hours afterward, there was a drop in fever to 101° and in forty-eight hours to 99° as seen in Fig. 2. With this drop in fever general improvement was noticed. The sputum diminished in quantity and was no longer foul. Patient was given 0.1 gm. of neosalvarsan on the first and fourth of November, 1930, and was discharged on

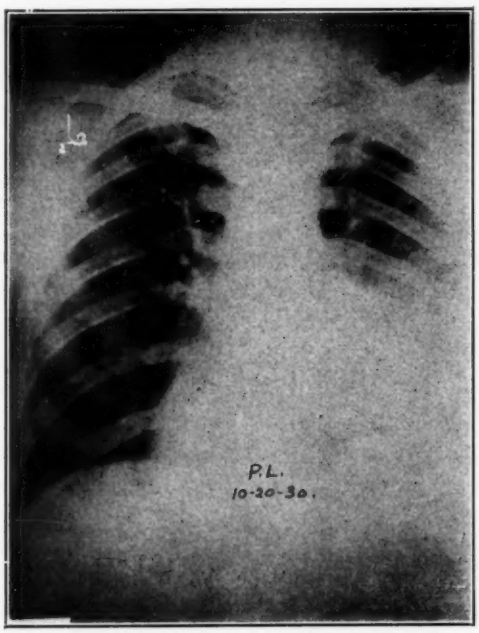

Fig. 4.

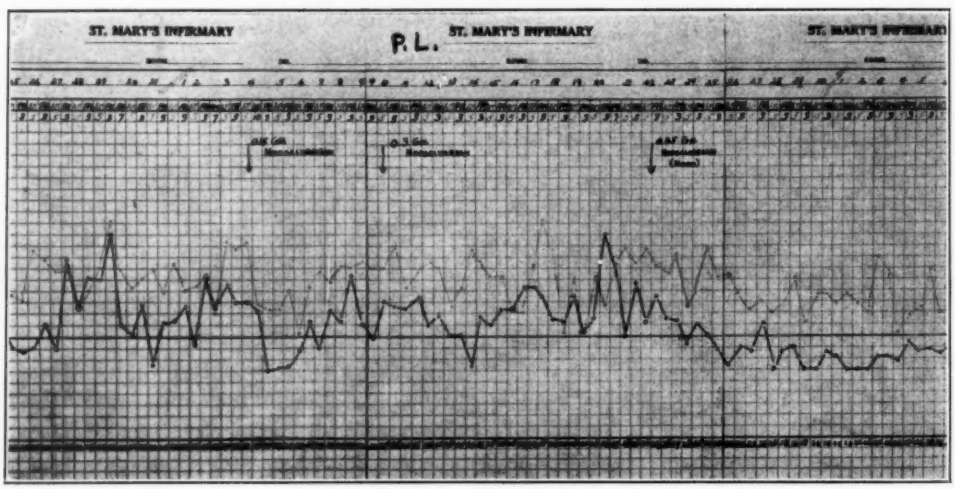

Fig. 5.

Jan. 2, 1931 very much improved. He was observed in the chest clinic until cured as seen in roentgenogram (Fig. 3). A reexamination on Jan. 7, 1932 revealed that the patient remained well.

CASE 2.—P. L., white male, aged twenty-six, admitted to hospital on Oct. 10, 1930 complaining of pain in right chest region, cough, loss of weight, tired feeling, fever, and

sweats, all these symptoms having been present since onset four weeks prior to his entrance into the hospital. He noticed no improvement while at home despite the fact that he was kept at complete bed rest. Temperature at entrance was 101°, pulse 120, respirations 24, W.B.C. 12,400, R.B.C. 4,830,000, hemoglobin 88 per cent. Arneth Schilling count showed a marked shift to the left. Sedimentation rate was rapid. Nonprotein nitrogen 29, blood sugar 98, Wassermann negative, urine negative, sputum negative for T.B., but revealed streptococci, pneumococci, *Micrococcus catarrhalis*, and gram-negative rods. Physical examination revealed definite limitation of motion on the right side, dullness and diminution of breath sounds and scattered indefinite râles from the fourth vertebral spine to base of right lung posteriorly. A roentgenogram (Fig. 4) showed an increase in density at base of right lung. A diagnosis of suppurative pneumonitis was made.

Patient was at first treated conservatively, but no improvement was noted after twenty-five days of such treatment. The afternoon temperature varied from 101° to 102°, pulse 100 to 120, and respirations 24 to 30. A roentgenogram showed a definite extension of

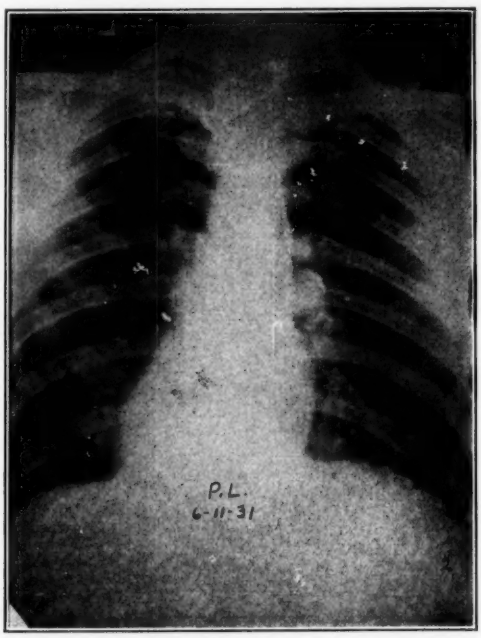

Fig. 6.

the process. Repeated dark-field examinations of sputum at this time revealed fusiform bacilli. On Nov. 5, 1930, twenty-five days after admittance, he was given 0.15 gm. neosalvarsan and within twenty-five hours, subjective improvement was noticed and also a temporary drop in the fever to 99.6°. Three-tenths grams of neosalvarsan was then given on Nov. 9, 1930, after which time the temperature again dropped temporarily to 100° as seen in Fig. 5. On November 22, thirteen days after, the second dose, 0.45 gm. of neosalvarsan was given after which time the temperature dropped to normal and the patient improved steadily to complete recovery as seen in Fig. 6.

CASE 3.—R. D., white female, aged twenty-seven, admitted to hospital on Nov. 5, 1930 with the following complaints: Weakness, loss of strength, pains in chest and lumbar region, chills and fever, shortness of breath. She was delivered of a baby two months prior to her entrance. A month following delivery she began to have chills followed by fever. Two weeks before entrance she began to have daily chills. Her physician diagnosed her condition as malaria, and she was treated for this condition. Failing to improve, she entered the hospital. Temperature varied from 97° in A.M. to 105.8° in P.M., pulse, from 90 to 130,

and respirations, from 20 to 28. W.B.C. 11,500, R.B.C. 3,470,000. Hemoglobin 85 per cent. Urine (noncatheterized) specimen showed 2-plus albumin, and a few pus cells. Catheterized specimen showed urine to be negative. Urine culture was negative. A Schilling count showed

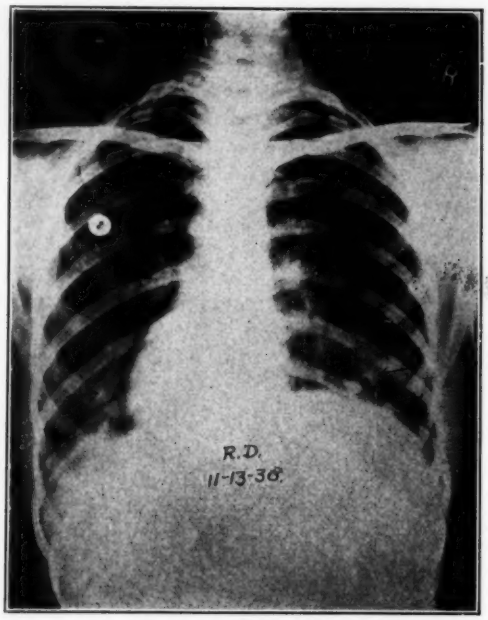

Fig. 7.

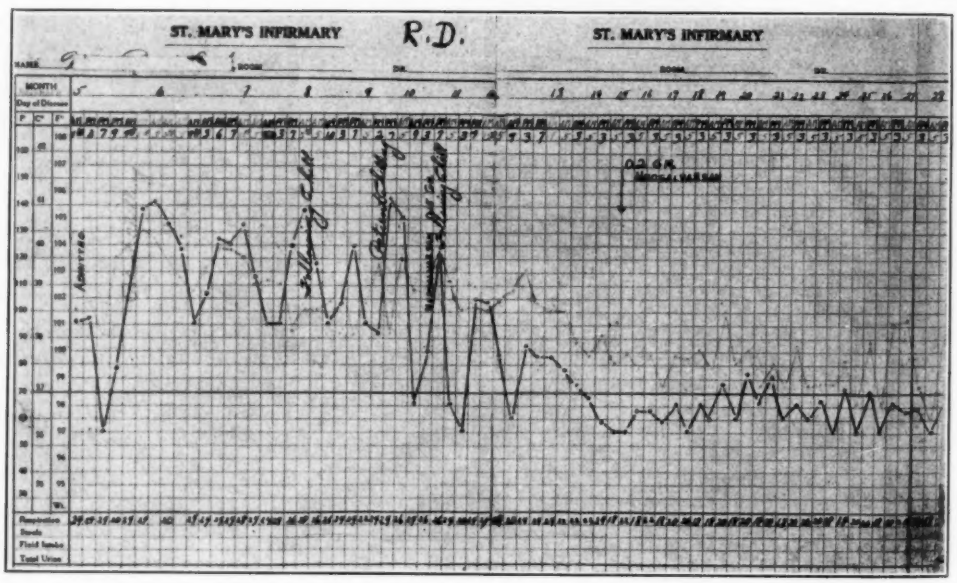

Fig. 8.

a shift to left and was negative for malarial parasites. Wassermann was negative. Nonprotein nitrogen was 29. Blood sugar was 91. Blood culture was negative. Stools revealed a yeastlike organism. Sputum showed numerous spirochetes and fusiform bacilli with the carbolfuchsin stain. Physical examination revealed the essential pathology to be in the

chest as follows: Dullness on percussion in lower one-third of both lungs, but especially on the left side. Harsh breath sounds in lower half of both lungs especially pronounced on left side. Scattered fine posttussive râles in lower half of both lungs. Bronchial breathing opposite sixth vertebral spine on the left side. Gynecologic examination by the gynecologic department failed to reveal any pathology in the pelvis to explain the chills and fever. A roentgenogram (Fig. 7) revealed a small area of density at base of left lung close to heart

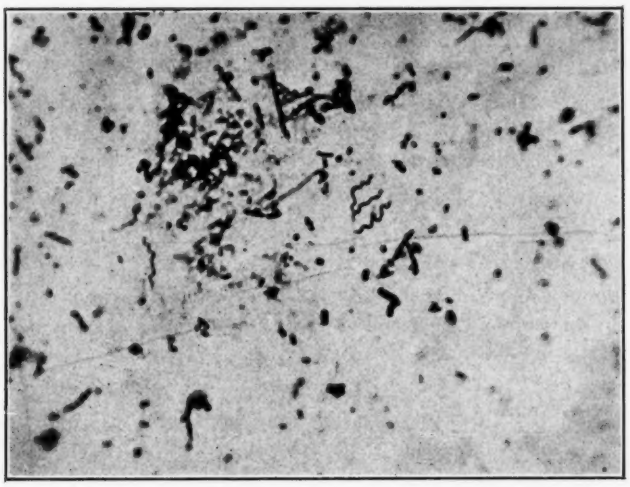

Fig. 9.—Anaerobes from a spirochetal empyema.

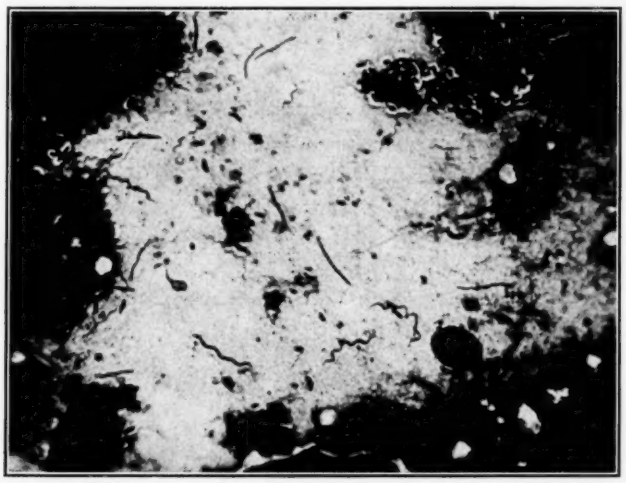

Fig. 10.—Anaerobes from the sputum of a case of spirochetal abscess.

and one suspicious shadow in second interspace. A diagnosis of multiple lung abscesses seemed to be justifiable under the circumstances.

Patient was treated for possible pyelitis with no results. Neosalvarsan was given 0.15 gm. on November 10, and temperature dropped to 102° the next day; the chills did not recur. In forty-eight hours the temperature dropped to 100°. Two-tenths gram was given on November 15, five days after first dose, and temperature dropped to normal the next day and remained normal as seen in Fig. 8. Clinical improvement was very rapid. Patient made a complete recovery later. In answer to a follow-up letter that was sent to her on Jan. 2, 1932, she stated that she had remained well.

The question that immediately confronted those who observed these cases was whether these striking results were actually due to the small doses of neosalvarsan or whether they were merely coincidental. It was decided to investigate this problem further, and in the fifteen months that followed a study of 22 additional cases of acute and chronic suppuration of the lungs, in whose sputum spirochetes were found, was made (Figs. 9 and 10).

The dosages used varied. Usually the initial dose in an adult was 0.15 gm. and was repeated every four days until such time when clinical improve-

TABLE I

FUSOSPIROCHETAL DISEASE (25 CASES)

TYPES OF LESIONS

1. Lung abscesses				
Acute	4	} Total		7
Chronic	3			
2. Abscesses complicated by gangrene				4
3. Suppurative pneumonitis				4
4. Bronchitis				
Acute	2			
Chronic	2	associated with syphilis	1 } Total	4
		associated with asthma	1	
5. Bronchiectasis and emphysema				1
6. Pulmonary T.B. complicated by fusospirochetosis				5
Total				25

TABLE II

RESULTS OF TREATMENT IN 25 CASES

Lung abscesses

(7) Cured 5

Improved 2 { Lost 1; Still under treatment 1

Abscesses complicated by gangrene

(4) Cured 1

Died 3 { 1 Multiple abscesses, spirochetal pneumonia, autopsy.
1 Multiple abscesses, empyema, sp. pericarditis with effusion, autopsy.
1 Gangrene and empyema, diabetes, operated upon.

Suppurative pneumonitis

(4) Cured 3

Improved 1

Bronchitis

(4) Cured 2

Improved 2 (chronic cases)

Bronchiectasis and emphysema

(1) Improved 1

Tuberculosis complicated by spirochetosis

(5) Improved 4

Died 1 Miliary T.B.

Total cases cured	10	40%
Improved	11	44%
Total cases cured or improved	21	84%
Died	4	16%
Total	25	100%

ment was marked and the sputum became negative for anaerobic organisms. At times the dose was increased to 0.3 gm., at other times it was decreased to 0.1 gm., and at other times to 0.05 gm. The number of injections given to an individual patient varied from one, in a case of acute putrid bronchitis, to fourteen, in a case of tuberculosis complicated by fusospirochetal infection. The total amount of the drug used in each case varied from 0.15 gram in the former, to 2.7 grams in the latter case.

The best results were obtained when the treatment was started early. Generally, it was noticed that the very sick patients responded to the treatment better if smaller doses were used.

DISCUSSION

A study of the results obtained with small doses of neosalvarsan in these cases leads to the pertinent question, as to whether the action of neosalvarsan was a specific one or whether the favorable results were merely accidental. An analysis of the clinical course of these patients before treatment, a study of the effect of neosalvarsan on the temperature curve, a further study of the rapid clinical improvement of the patients, and a still further study of the roentgenograms before and after treatment, scarcely justifies the consideration of accident as a plausible explanation for the favorable results obtained. It follows, therefore, that the results secured might have been due either to direct spirillicidal action or to an indirect tonic action.

That neosalvarsan has an indirect specific spirillicidal action on the *Treponema pallida* and a nonspecific tonic effect on the host had long been known. It is, therefore, not unreasonable to conclude that in fusospirochetosis the arsenicals in general, and neosalvarsan in particular, may have the same action on the mouth spirochetes and on the host respectively, especially so, since the *Treponema pallida* and the buccal spirochetes are so closely related.

The preceding observations further suggest the query as to whether small doses of neosalvarsan are more effective in the treatment of fusospirochetosis than the larger doses which are recommended in the literature. In answer to this question, it must be stated that while there is no direct evidence in favor of small doses, there is considerable indirect clinical and some experimental proof in this direction which should not be ignored.

A clinical study of the effect of large and small doses of neosalvarsan on the course of the disease in other febrile and toxic lung conditions reveals suggestive evidence in favor of small doses. For instance, it is common knowledge that the treatment of syphilis complicated by active tuberculosis with large doses of neosalvarsan is only rarely followed by improvement. On the contrary, the patients are usually made worse. It is for this reason that there is a strong tendency on the part of phthisiologists to advocate[25, 26, 27, 28] the use of small doses of the arsenicals in the treatment of coexistent syphilis and active tuberculosis.

Further proof in this connection is the fact that there is a growing realization on the part of syphilologists that large doses may do more damage than good. Schamberg,[29] for instance, in a relatively recent article, advocates the use of small doses of the arsenicals in the treatment of syphilis in preference

to large doses. The report of the Salvarsan Council of Great Britain[30] and the recent article by Cole[31] and coworkers definitely points to the fact that accidents in the treatment of syphilis are most common when large doses are used.

The most important proof in favor of small doses, however, is the experimental work of Toyama and Kolmer[32] who have shown that large doses of either arsphenamine or mercury directly interfere with the nonspecific defense, and diminish the production of agglutinins and lysins with which the body carries on its own defense against the invader. On the other hand, minute doses have a definitely stimulating effect on the patient and seem to encourage the formation of agglutinins and lysins.

In summarizing the possible action of small doses of neosalvarsan in the treatment of fusospirochetosis, it is conceivable that the salvarsan, through its specific spirillicidal action, kills the spirochetes, and through its nonspecific tonic action stimulates the formation of agglutinins and lysins which in turn destroy the other members of the symbiotic group.

I am greatly indebted to Dr. G. O. Broun, Dr. R. Kinsella and Miss E. McGarry for their assistance and encouragement in this work.

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UNIVERSITY CLUB BUILDING

THE GROWTH OF PATHOGENIC BACTERIA IN IMMUNE BLOOD*

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WHEN one consults a text on the cultivation of pathogenic microorganisms from the blood stream, it is generally stated that the procedure consists of withdrawing from 10 to 20 c.c. of blood from a vein and injecting this into 50 to 100 c.c. of broth culture medium, and that this large quantity of culture medium is necessary to dilute the antibodies in the serum, the antibodies being bactericidal. The directions, also, generally state that 5 c.c. of blood may be added to 10 c.c. of melted agar culture medium and plated. Other procedures may call for the addition of the blood to citrated or bile culture medium, the addition of these agents to the broth culture being to destroy the bactericidal action of the blood, particularly the serum. Stitt[1] gives the following technic: "As a receptacle for the blood we employ Erlenmeyer flasks of 100 c.c. capacity, containing 10 to 25 c.c. of salt solution with 1 or 2 per cent of sodium citrate, for prevention of coagulation. In this way we may take from 10 to 25 c.c. of blood. For plates add 2 or 3 c.c. of this citrated blood to 6 or 8 c.c. of melted agar at 45° C. Finally we place the receiving flask in the incubator and culture it as well as the other media. Some organisms do not develop in this citrated blood, possibly on account of the blood concentration. This can be avoided by adding 50 to 75 c.c. of bouillon to the citrated blood remaining in the flask. For culturing blood in septicemic conditions use at least ten times as much bouillon as blood."

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Muir and Ritchie[2] state: "In making blood cultures in order to detect the presence of enteric bacilli 5 c.c. of blood are added to 10 c.c. of sterilized ox bile or 50 c.c. of a 0.5 per cent solution of bile salts in 1 per cent sodium citrate. In examining for other organisms, e.g., streptococci, 5 or 10 c.c. of blood are added to a large quantity of fluid medium (100 c.c. or more)."

Clawson[3] draws 50 c.c. of blood and distributes this in two tubes and allows the blood to clot. The serum is withdrawn and the clot removed to 250 c.c. of dextrose beef infusion broth. He states that the firm clot seems to favor a partial anaerobic culture, and at the same time any antibodies that may be present are diluted in the fluid medium.

Cecil, et al.[4] withdraw 20 c.c. of blood and divide into two tubes. After the clot has formed the serum is withdrawn, the clot broken and transferred to 50 c.c. of beef heart infusion broth. This procedure is used to rid the culture of antibodies.

Mesnil[5] reported, in 1898, that the serum of rabbits which had been immunized against *Bacterium erysipelatis suum* makes an excellent medium for the culture of this microorganism.

Bridré and Jouan[6] showed that the observation of Mesnil was also true in regard to horses, and that the *Bact. erysipelatis suum* grew better in the immune serum than in the serum of normal horses. These authors found that the growth in the bouillon which contained the immune serum (10 to 20 per cent) was about six times as great as that containing an equal amount of normal horse serum.

This phenomenon was studied by Nicolle and Césari.[7] These authors found that the best culture medium was one made of Martin's bouillon 9 parts and immune serum one part. The organisms studied were anthrax, tetanus, gonococcus, diphtheria, typhosus, paratyphosus A, and pneumococcus Types I, II and III. All of these bacteria grew more abundantly in the medium containing the homologous immune serum. The growths of the gonococcus and the pneumococcus were not as readily apparent as the growths of the other microbes, but there was some better growth in the medium containing the immune serum. Some of the organisms grew so abundantly as to form a scum on the surface of the medium; such does not occur in the ordinary culture media.

The phenomenon that concentrated immune serum is not bactericidal in vitro has been known for years. This is called the "phenomenon of Neisser and Wechsberg." These authors found that there was no bactericidal action on the typhoid bacillus when the typhoid immune serum was added to an equal amount of a typhoid culture, but that there was a bactericidal effect when the immune serum was diluted, and that this effect was lost when the dilution reached a certain figure.

Relative to this phenomenon Muir and Ritchie,[2] page 209, state: "It is to be noted that in the case of a bactericidal serum there is an optimum amount of immune-body which gives the greatest bactericidal effect with a given amount of complement. If this amount of immune-body by exceeded, the bactericidal action becomes diminished and may be practically annulled. This

result, which is generally known as the 'Neisser-Wechsberg phenomenon,' has been the subject of much controversy, and cannot yet be said to be satisfactorily explained; it is apparently of the nature of a 'zone phenomenon.' "

Bolton[8] found that normal serum may kill relatively more bacteria when diluted than when undiluted.

Neisser and Wechsberg[9] state that if the immune serum be greatly diluted its action is changed and it loses its general bactericidal power and develops a marked increase in the destructive action upon the homologous organism.

EXPERIMENTAL

In order to test out some of the above statements rabbits were immunized with *B. typhosus, B. abortus,* and a streptococcus. The titers of these sera were 1:6400, 1:3200, and 1:100 respectively. The sterile sera were placed in sterile tubes and inoculated with the homologous organism. The growth was profuse in all of the cultures. Blood was also withdrawn from each rabbit and defibrinated by the use of a sterile Erlenmeyer flask which contained broken glass; a separate flask was used for each rabbit. Each defibrinated blood was inoculated with its homologous organism. The organisms grew abundantly in these media.

The blood serum of a patient having a titer of 1:25000 for *B. typhosus* was available, at this time, as was the organism isolated from the patient. The undiluted sterile serum was inoculated with the homologous organism. The organism grew so abundantly that it formed a scum on the surface of the medium. The growth was so rank in the three tubes which were used that it was at first thought that the serum was contaminated. This experiment was repeated with other strains of *B. typhosus* and the same phenomenon occurred. Other cases of typhoid fever became available as time went on and this same procedure was followed with the same results.

It was decided to apply the above facts to the isolation of microorganisms from the blood stream, i.e., blood cultures. The technic consisted of withdrawing 20 c.c. of blood and discharging 5 c.c. into each of two culture flasks containing 50 c.c. of veal heart infusion broth, and the remaining 10 c.c. were discharged into an Erlenmeyer flask of 50 c.c. capacity containing broken glass (glass beads may be used) to defibrinate the blood. In several experiments a 100 c.c. flask was used and 20 c.c. of blood placed in the flask. The flask containing the defibrinated blood was placed in the thermostat like any other culture. The flasks were examined and transplants made as usual.

It is apparent that there are but a given number of bacteria per cubic centimeter of blood in a blood stream infection, and in carrying out an investigation with standard methods for controls it is possible that the bacteria may be present only in the blood discharged into the defibrinating flask; it is likewise possible for the organism to be discharged from the syringe only into one of the flasks containing the broth; however, no culture, to date, has been obtained in the broth and not in the defibrinated blood, while the reverse has occurred on a number of occasions.

The following organisms have been isolated from the blood stream by the defibrinated blood technic: *B. typhosus, B. paratyphosus B, B. abortus,* gonococcus, *M. catarrhalis,* and streptococcus.

COMMENT

The literature on the methods of taking blood cultures assumes that whole blood is bactericidal, due to the serum. The work of Neisser and Wechsberg shows that this is not the case. This is further substantiated by the work of Nicolle and Césari who found that the immune serum stimulated the growth of the homologous organism. It appears to me that it is but logical to assume that such would be the case, inasmuch as the infecting agent is living in the blood stream, or at least in the tissues served by the blood, and that in vivo, at least, this makes a most excellent medium; a better medium, perhaps, than the blood of a normal animal, or individual in the case of human beings. The above experiments seem to bear out this assumption.

The work of some investigators would indicate that the bactericidal zone of the serum is that in which most of the cultures are diluted in the standard methods. Due to the number of positive cultures obtained in this zone, it appears that the bactericidal zone varies widely.

The use of defibrinating flasks for blood cultures simplifies the taking of these cultures and gives a satisfactory medium for the infecting organism. The defibrinated blood may be covered with a layer of oil for the cultivation of anaerobes, although, experimentally, anaerobes were grown in the defibrinated blood without oil by using a small flask and withdrawing an extra amount of blood to give extra depth of medium for anaerobic conditions.

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LABORATORY METHODS

AN AUTOMATIC AND GRAPHIC METHOD OF RECORDING DIURESIS*

W. E. GOWER, CHICAGO, ILL., AND J. VAN DE ERVE, CHARLESTON, S. C.

IN CONNECTION with experiments on the relationship of diuresis to recovery from barbital poisoning reported elsewhere by us,[1] we looked about for a suitable method for recording the rate of urine flow from barbitalized dogs over an extended portion of the recovery period. The nature of the experiments was such that it was necessary to know whether a given urine volume collected over an eight- to twenty-four-hour period represented uniform renal

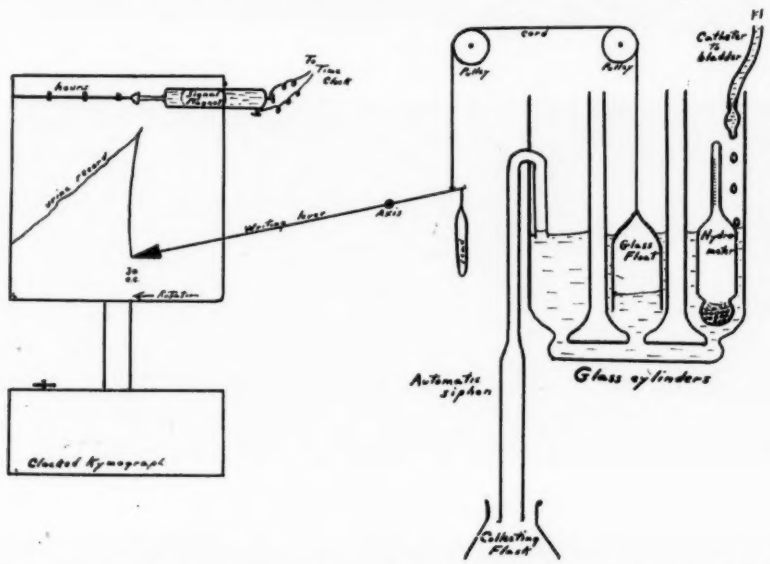

Fig. 1.—Apparatus for recording the rate of urine output. For explanation see text.

performance over the entire period or an increasing, decreasing, or fluctuating rate of flow. To suit our needs the record should be condensed, graphic, continuous, and automatic to the extent of not requiring constant or even exactly periodic attention on the part of the laboratory staff, and should permit fairly accurate calculation of the rate of flow for any increment of time. None of the existing devices with which we became familiar answered these requirements and the success of the method to be described was sufficient, perhaps, to warrant description.

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The female dogs used in these experiments were prepared by perineorrhaphy so that the urethra was easily accessible for catheterization. In most of the experiments barbital anesthesia was obtained before the records were started, but a few records were made in nonanesthetized animals trained to lie quietly and submit to the administration of fluids and diuretic or anti-

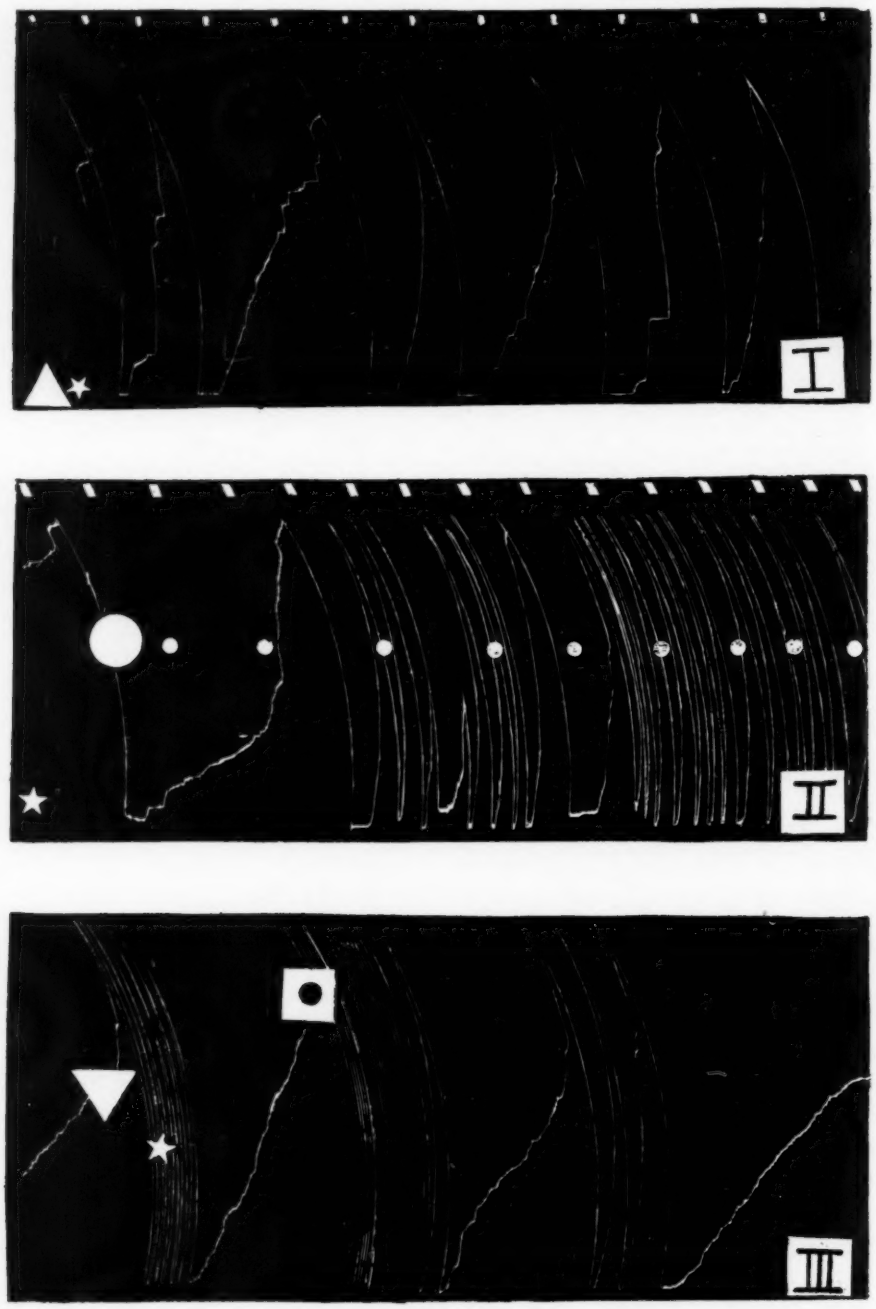

Fig. 2. (See legend on opposite page.)

diuretic principles. Under the experimental conditions the rates of urine flow varied from less than 2 to over 60 c.c. of urine per kilogram per hour in animals weighing from 5 to 20 kg.

In principle, the method consists of collecting the urine through a retention catheter adjusted in the bladder into a cylinder containing a float, the rise of which is recorded by means of a suitable lever system and writing point on a smoked drum moving about 2½ cm. per hour. At the top of the excursion the cylinder is automatically emptied, returning the writing point to the base line for another trip.

The method allows of considerable variation and refinement. Our arrangement is diagrammed in Fig. 1, showing three upright parallel cylinders with communication at their bases, one for receiving the urine, one for operating the float, and a third for emptying the apparatus intermittently by siphon. Each excursion represents approximately 35 c.c. of urine. For clearness of illustration it is represented as being an all glass one piece apparatus; actually it was assembled by means of T-tubes, rubber tubing and glassware as found in the average laboratory.

In the use of the apparatus the greatest technical difficulty encountered is in the adjustment of the siphon to empty the cylinders with uniform excursions and urine volumes, and an electromechanical arrangement may eventually prove more satisfactory. The tendency for a few drops of liquid to become dispersed along the siphon tube and by their weight cause premature emptying, is reduced by extending the siphon tube with a larger glass or rubber extension to a flask several feet below the level of the table or on the floor. This extension accelerates the emptying process by the greater pull of the longer liquid column, draws fewer interspersed drops of fluid into the constricted upper portion of the siphon tube, and those lodging in the expanded portion drain down the walls of the tube establishing an air column without tendency to start the emptying mechanism. Before each experiment we have found it best to adjust the writing point to the newly smoked drum, and by introducing water into the apparatus, produce several satisfactory excursions before starting the record.

Three typical records of urine flow are shown in Fig. 2. These experiments are discussed in the paper previously referred to. Occasional right angle steps in the urine records are artefacts due to imperfect adjustment of

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Fig. 2.—Graphic records of urine flow recorded by apparatus shown in Fig. 1. Weight of animal: 11.9 kilograms. Dose of sodium barbital: 4.0 grams given intravenously in 10 per cent aqueous solution on each occasion.

KEY: I. Record of urine flow from 10:45 A.M. to 10 P.M. Apr. 10, 1931.
△ 500 c.c. 0.9 per cent sodium chloride solution by stomach tube.
* Injection of sodium barbital.

II. Record of urine flow from 11 A.M. Apr. 17, 1931 to 12:30 A.M. Apr. 18, 1931.
* Injection of sodium barbital.
○ Intravenous drop injection of 1000 c.c. of 10 per cent glucose started.
o Completion of 1000 c.c. increments of above.

III. Record of urine flow from 9.45 AM. Mar. 27, 1931, to 1:30 A.M. Mar. 28, 1931. Record started in unanesthetized animal.
▽ 500 c.c. of water given by stomach tube.
* Injection of sodium barbital.
⊡ Intravenous injection of 1000 c.c. of 10 per cent glucose in fifteen minutes.

the level of the catheter in the bladder and may be eliminated by the use of the expanded retention catheter used in bladder surgery.

We wish to acknowledge the aid of Dr. A. J. Carlson in arranging this material for publication.

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A STUDY OF THE EAGLE ANTIGENS FOR WASSERMANN AND FLOCCULATION TESTS*

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THE history of the serology of syphilis is rich in its variety of antigens. Ever since the introduction of an alcoholic extract of normal tissues[1] as an antigen for complement fixation in syphilis, numerous variations of this basic extract have been suggested to produce a more satisfactory and more sensitive antigen. If one could disregard the possibility of false positive reactions due to its intense anticomplementary action, a highly sensitive antigen could be prepared with comparative ease. To insure a margin of safety from false positive fixations, it has been our practice to use only antigens whose antigenic units (the minimum amount of antigen which will produce complete inhibition of hemolysis in the presence of known four-plus sera) are not more than $\frac{1}{100}$ of the anticomplementary unit for that antigen (minimum amount of antigen producing inhibition of hemolysis in the absence of positive sera).

As a routine antigen for the Wassermann test, we use the Kolmer antigen prepared from a cholesterinized alcoholic extract of powdered beef heart.[2] Each specimen of blood serum submitted to our laboratories for serum diagnosis of syphilis is tested by both Kahn and Kline precipitin methods in addition to the Wassermann test. Although we occasionally find a serum which is positive in a Wassermann test and negative in the precipitin test, generally speaking the precipitin reactions appear more sensitive than the Wassermann reaction. The hemolytic system for the Wassermann test is adjusted to maximum sensitivity and a margin of elasticity allowed for by using two units of complement and two units of amboceptor. These units are determined by graded titrations of the two reagents, using as a unit the smallest amount producing complete hemolysis after one-half hour at 37.5° C.

In November, 1930, Eagle of Johns Hopkins University Laboratories published a paper[3] explaining the fortifying effect of cholesterin upon antigens

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used in serum diagnosis of syphilis. Subsequent to this (May, 1931) he published another paper[4] describing a more sensitive antigen for use in the Wassermann reaction. In May, 1932, the same author published a paper[5] describing the new flocculation test for syphilis.

In our laboratory, under the guidance of the senior author, there was made a study of the comparative values of the Eagle and Kolmer Wassermann antigens, and the Eagle, Kahn, and Kline precipitin tests.

The Kolmer antigen for Wassermann tests is somewhat tedious to prepare and not infrequently freshly prepared Kolmer antigens must be discarded because of insufficient antigenic property or too great anticomplementary activity. Eagle's Wassermann antigen is quite simple to prepare, and to date the authors have had no unsatisfactory lots of antigen prepared by this method.[4] The increased sensitivity of this antigen is dependent on a high concentration of antigen-lipoids reinforced by 0.8 per cent cholesterin and 0.6 per cent sitosterol.

Wassermann Technic.—To 0.1 c.c. of freshly inactivated blood serum is added 0.4 c.c. of Reagent A (ten units of antigen and two units of complement in 0.9 per cent NaCl). To a second tube containing 0.1 c.c. of the same serum is added 0.4 c.c. of Reagent B (two units of complement in 0.9 per cent NaCl). Control tubes containing 0.1 c.c. of 0.9 per cent NaCl and 0.4 c.c. of Reagents A and B respectively are placed in the rack with the sera to be tested. These are incubated for two hours at 8° C. To each tube is added 0.5 c.c. of 2 per cent sensitized cells (sensitized immediately before use) containing two units of amboceptor. The tests are then incubated in the water-bath at 37.5° C. until the two reagent controls are completely hemolysed and are left in the water-bath for ten additional minutes before reading. Although Eagle recommends the use of 0.2 c.c. of a 1-200 dilution of antigen without titration, in accordance with our customary procedure we titrated the antigen and used ten antigenic units as a dose.

From our serologic work we tested 1081 cases taken at random, giving no consideration to the case histories before testing. Each of these was tested by Kline's precipitin test, by Kahn's precipitin test (using one quantity of antigen only, 0.025 c.c.) and by Wassermann tests using Kolmer's and Eagle's antigens respectively, and the technic described above. Of the 1081 cases tested, 458 were positive by Kline's test, 346 were positive by Wassermann employing Eagle's antigen, 325 were positive by Kahn's test and 266 were positive by the Wassermann employing Kolmer's antigen. There were no positive K.A.W. (Kolmer antigen Wassermanns) unaccompanied by other positive serology (Kahn, Kline, or Eagle). Likewise there was only one positive Kahn in the absence of other positive serology; this was a treatment check case. Of the Klines, there were 66 positives with no other positive serology. Of these 58 were one-plus (one-plus reactions in any one test unaccompanied by other positive serology are not customarily reported by our laboratory), and 8 were higher positives. Their case histories were as shown in Table I.

TABLE I

	DIAGNOSIS	TREATMENT CHECK	NO HISTORY ON CARD
3-plus	1	1	1
2-plus	0	2	3
1-plus	25	9	24

There were 12 E.A.W. (Eagle antigen Wassermanns) which gave a one-plus reading in the absence of any other positive serology, and 9 higher positives distributed as shown in Table II.

TABLE II

	DIAGNOSIS	TREATMENT CHECK	NO HISTORY ON CARD
4-plus	0	1	1
3-plus	1	1	0
2-plus	3	1	1
1-plus	6	3	3

These results seemed to indicate a sensitivity of the E.A.W. approximately 1.3 times that of the K.A.W., with only a small percentage (21 out of 1081 tests) pointing to possible false positives. There were 325 E.A.W. accompanied by other positive serology, and 324 Kahn tests accompanied by other positive serology. The Kline test was somewhat more sensitive, having 400 positives accompanied by other positive serology. The specificity of these tests could not accurately be estimated by the above method of case selection, due to the fact that many of these cases were only submitted for a single examination and in most cases accompanied by very inadequate history. We therefore selected a number of known syphilitics from the skin clinics of the Indianapolis City Hospital and Fort Benjamin Harrison Hospital.

The ideal type of case would have been those showing early primary lesions, but these cases present themselves very infrequently. From the group of patients in the City Hospital clinics, we were able to secure only three primary cases. One of these, C.P., had been dark-field positive and serologically negative. After three treatments we tested his blood with the following results: K.A.W. four-plus, E.A.W. four-plus, Kahn negative, and Kline negative. A recheck four days later showed K.A.W. two-plus, E.A.W. three-plus, Kahn negative, and Kline negative. This was one of the rare cases in which there appears a greater affinity for the complement fixation phenomena than for the flocculation phenomena. A second case was that of G.A., dark-field positive and with the following serologic findings: K.A.W. negative, Kahn negative, Kline negative, and E.A.W. three-plus. A quantitative E.A.W. (0.1 c.c., 0.05 c.c., 0.025 c.c., and 0.005 c.c. respectively) read three-plus, three-plus, two-plus, and two-plus. A third patient, C.S., having a positive dark-field had the following serology: K.A.W. two-plus, E.A.W. two-plus, Kahn three-plus, and Kline two-plus.

TABLE III

PATIENT	NUMBER OF TEST	K.A.W.	E.A.W.	KAHN	KLINE
1. L.B.	1	Neg.	3-plus	2-plus	2-plus
	14 day interval				
	2	Neg.	4-plus	Neg.	4-plus
2. C.C.	1	1-plus	2-plus	2-plus	Neg.
	14 day interval				
	2	2-plus	4-plus	2-plus	4-plus
3. H.C.	1	Neg.	Neg.	Neg.	2-plus
4. W.C.	1	Neg.	2-plus	Neg.	Plus-minus
5. C.D.	1	1-plus	3-plus	4-plus	2-plus
	17 day interval				
	2	Neg.	1-plus	Neg.	Neg.
6. M.F.	1	Neg.	2-plus	3-plus	4-plus
7. T.G.	1	Neg.	Neg.	Neg.	Neg.
	12 day interval				
	2	Neg.	Neg.	Neg.	Neg.
8. H.G.	1	Neg.	Neg.	Neg.	Neg.
	12 day interval				
	2	Neg.	Neg.	Neg.	Neg.
9. R.G.	1	Neg.	Neg.	Neg.	Neg.
	12 day interval				
	2	Neg.	Neg.	Neg.	Neg.
10. A.G.	1	Neg.	Neg.	Neg.	Neg.
11. R.H.	1	1-plus	4-plus	Neg.	2-plus
12. A.H.	1	Neg.	4-plus	3-plus	2-plus
13. E.H.	1	Neg.	4-plus	4-plus	4-plus
14. O.H.	1	Neg.	2-plus	Neg.	2-plus
15. B.L.	1	Neg.	4-plus	4-plus	4-plus
16. M.L.	1	Neg.	3-plus	2-plus	4-plus
	2 day interval				
	2	Neg.	Neg.	2-plus	4-plus
17. P.M.	1	Neg.	1-plus	Neg.	1-plus
18. A.M.	1	Neg.	Neg.	Neg.	Neg.
19. G.N.	1	Neg.	Neg.	Neg.	Neg.
20. B.N.	1	Neg.	Neg.	Neg.	Neg.
21. M.P.	1	Neg.	1-plus	Neg.	Plus-minus
	2 day interval				
	2	Neg.	Neg.	Neg.	Plus-minus
22. W.R.	1	Neg.	1-plus	Neg.	1-plus
23. L.R.	1	Neg.	4-plus	4-plus	4-plus
24. E.R.	1	3-plus	4-plus	Neg.	2-plus
25. S.R.	1	Neg.	Neg.	Neg.	Neg.
26. D.S.	1	Neg.	4-plus	Neg.	Neg.
	14 day interval				
	2	4-plus	4-plus	2-plus	4-plus
27. J.S.	1	Neg.	1-plus	Neg.	4-plus
28. P.S.	1	Neg.	Neg.	Neg.	Neg.
	7 day interval				
	2	Neg.	Neg.	Neg.	Neg.
29. R.S.	1	Neg.	Neg.	Neg.	Neg.
30. J.S.	1	Neg.	4-plus	4-plus	4-plus
	7 day interval				
	2	Neg.	Neg.	4-plus	3-plus
31. E.T.	1	Neg.	Neg.	Q.N.S.	Neg.
	11 day interval				
	2	Neg.	Neg.	Neg.	Neg.
32. B.T.	1	Neg.	3-plus	Neg.	4-plus
	11 day interval				
	2	Neg.	3-plus	4-plus	1-plus
33. O.T.	1	Neg.	3-plus	Neg.	2-plus
34. M.Y.	1	1-plus	4-plus	4-plus	2-plus
35. J.W.	1	Neg.	Neg.	Neg.	Neg.
36. Z.W.	1	1-plus	4-plus	4-plus	4-plus

We tested four cases of primary syphilis from Fort Benjamin Harrison. All four had been diagnosed on positive dark-fields and immediate treatment instituted. Two separate testings twelve days apart revealed no positive serology.

Thirty-six "treatment check" cases were tested serologically. The results are tabulated in Table III.

The above results show a close coincidence between the E.A.W. and the precipitin tests. The figures in Table III show a sensitivity of the E.A.W. 3.5 times as great as that of K.A.W. Cases 5 and 26 are the only incidences of a positive E.A.W. in the absence of all other positive serology. The latter developed positives in all three other tests after an interval of fourteen days. The senior author had suggested the possibility that the antigen might prove so sensitive that it would hold a positive indefinitely in treated cases. It was with this possibility in mind that the above series of treated cases was tested, and from the results of this series, we believe we can state that such is not the case. As a further check on this point we ran all four tests on 74 treatment check cases showing completely negative serology by our routine tests. Two of these gave a 1-plus E.A.W., one a 2-plus, and one a 4-plus E.A.W. The others were negative by this test also. Twenty normal individuals were tested by all four serologic procedures and were all negative in every test.

CONCLUSIONS

After having submitted the Eagle Wassermann antigen to the test routine described above, we are convinced that it is a more sensitive antigen than the Kolmer antigen, and that tests in which this antigen is employed correspond very closely to the Kahn and Kline precipitin tests in degree of sensitivity. We believe that in this series of tests it has not proved too sensitive.

THE EAGLE FLOCCULATION TEST

An antigen for this test was prepared according to Dr. Eagle's directions[5] and one thousand sera treated in the manner he described; K.A.W., Kahn, and Kline tests were done on each specimen. Strong positives and negatives could be very easily and accurately read by this test, but the intermediate zone, which Dr. Eagle characterizes as "doubtful," we were unable to read satisfactorily. Accurate readings of low positives were certainly no easier for us than in the case of a one-plus or two-plus Kahn test. We found in the case of strongly positive sera that this test checked very closely with the other serologic tests. Cases showing a negative Wassermann test and two-plus or three-plus Kahn and Kline were rarely positive by the Eagle Flocculation method. The method is more time-consuming than either the Kahn or Kline method for precipitin tests. Therefore, with the exception of this brief survey, no further work was done with this test.

We acknowledge with gratitude the cooperation of the clinicians of the Indianapolis City Hospital Skin Clinic and the Medical Staff of Fort Benjamin Harrison.

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AN EASILY ASSEMBLED, SELF-RECORDING PERFUSION APPARATUS*

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THIS apparatus was devised for the study of the volume of blood flow through the cat's carotid at fixed pressures over long periods of time, but may prove useful for other types of perfusion.

The fundamental mechanism employed is the "Autopulse" (Fig. 1), a device used to pump fuel from the tank to the carburetor of internal combustion engines. It may be obtained at a reasonable price through dealers in electrical automobile equipment. The device consists of a small metal bellows pump of about 0.8 c.c. capacity intake and outlet valves. The bellows is filled by the action of an electromagnet, which pulls against a spring. The spring expels the contents of the bellows at a constant pressure, and at the end of the stroke, contact is closed, which actuates the electromagnet once more. Current is supplied by a storage battery.

To adapt the "Autopulse" to physiologic purposes, it is necessary in the first place to introduce a means of adjusting the pressure. This is done by placing a thin nut between the spring and the arm which supports it and threading a machine screw into it. The end of the screw projects through a hole drilled in the bottom of the sheet metal casing. By turning the screw, the pressure may be adjusted from about 80 to about 250 mm. of mercury.

Next it is essential to arrange an electrical signal to register each stroke of the pump. This is done by soldering the tips of a separate pair of wires in shunt with the electromagnet. The wires run to a signal magnet on the special kymograph to be described below.

Finally, a constant supply of blood from a heparinized animal must be provided. This is derived in the present instance from cannulas in both fem-

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oral arteries. To insure that the amount necessary for each stroke is always available and that no more than essential is abstracted from the circulation, a float valve is required. The float chamber consists of a glass tube about 2.5 cm. in diameter, closed at one end by a two hole stopper. A short piece

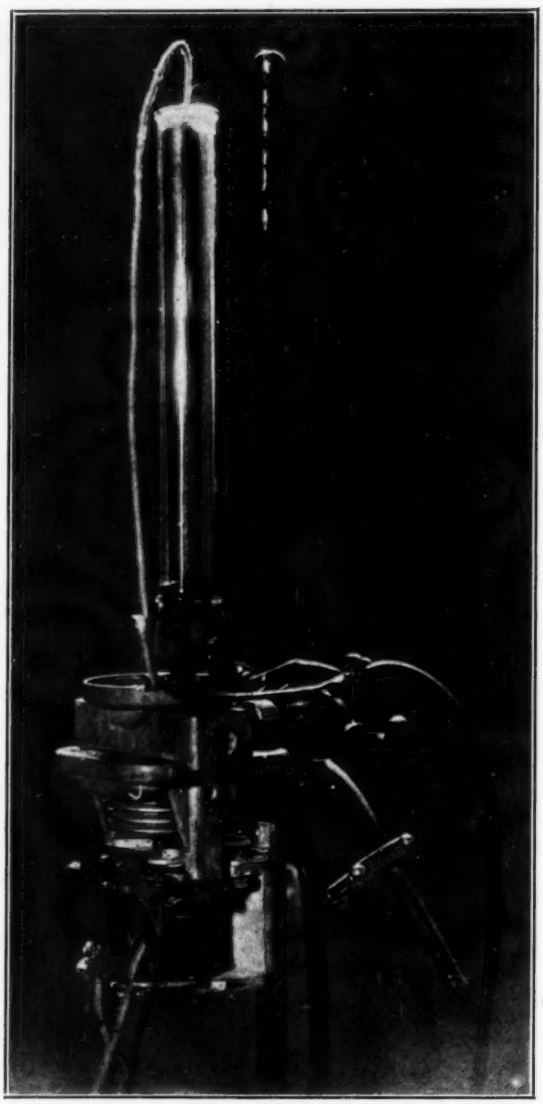

Fig. 1.—"Autopulse" provided with glass float chamber and float (above). To the right, leading to the float chamber, is the rubber tube and check valve. The outlet, connected to the carotid, is on the further side. The black wires lead to the signal magnet, the white wires to the battery. Notice that both are attached to the same terminal at the base of the solenoid, but that they are attached to opposite sides of the contact points above.

of copper tubing occupies one hole, and is soldered into the intake valve chamber of the pump (after the gasoline filter has been removed, and its projecting support sawed off level). An L-tube leads into the other hole, carrying at its further extremity an improvised cut-off valve. As is illustrated in Fig. 2, this

consists of a length of thinnest rubber tubing, 3 mm. in diameter, which runs between two wire rings fixed permanently in line. On a straight stub of wire at right angles to the axis of the tube, a wire crank is pivoted in such a way that its short arm compresses the rubber tubing when its long arm is elevated. The long arm is actuated by a J-shaped wire, which hooks over the side of the float chamber and rests upon the float. The float consists of a paraffined wood or pasteboard box (a small shaving-soap box would do) 5 to 10 cm. long, fitting easily in the float chamber. When it rises on the column of blood in the chamber, the flow from the femoral is cut off.

It is difficult to guard against the entrance of bubbles of air into the pump. To prevent embolism, the blood is passed from the outlet of the pump into a small inverted bottle, of about 20 c.c. capacity, and out again to the carotid cannula. If any air collects at the top of the bottle, it may be removed by a lumbar puncture needle inserted through the cork. A thermometer also lies in this chamber.

In some experiments the blood was warmed by passing through a coil of fine brass tubing in a thermostated jar; but a much simpler means of heating the air trap, such as an electric bulb placed near it, will suffice for most purposes.

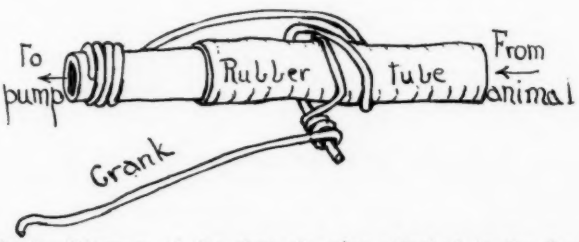

Fig. 2.—Diagram of the shut-off valve attached to the float.

The systolic and diastolic pressures at which the blood is delivered are read off on a mercury manometer, connected to the outlet by a T-tube. The carotid pressure and temperature are not registered directly, as they should be constant, but are written into the record from time to time during the experiment.

The output of the pump varies slightly with different pressures and should be measured directly under the particular conditions which exist for each series of experiments.

Before this perfusion pump had been a week in use, it became obvious that some special means of recording would have to be developed. The paper on an ordinary long kymograph was used up before a base line was established, unless it was run so slowly that individual strokes of the pump were difficult to distinguish, and the ordinary ribbon recorders are not adapted to register alterations in blood pressure. The following apparatus was therefore devised (Fig. 3) using inexpensive ready-made materials whenever possible.

The whole kymograph is mounted on a board 10 inches wide and 30 inches long. Rolls of adding machine paper, three and a half inches wide,

are used to take the record. The paper is suspended on a roller at one end of the board and passes at once under a bridge which carries two of the signal-magnets. It then runs far enough to allow the inked record to dry, before reaching the propelling mechanism.

The kymograph mechanism itself is built mostly from the gear box of an "Erector" set, obtainable at any toy shop. The paper is pulled by three wheels each composed of two of the discs intended to form the wheels of the toy automobile which can be built from the set. Slipping is prevented by flat "tires" of appropriate-sized rubber bands cemented to the circumference. The strip of paper slides upon a piece of celluloid which is bent around the front of the wheels so that the paper is in elastic contact with a full quadrant of their surface.

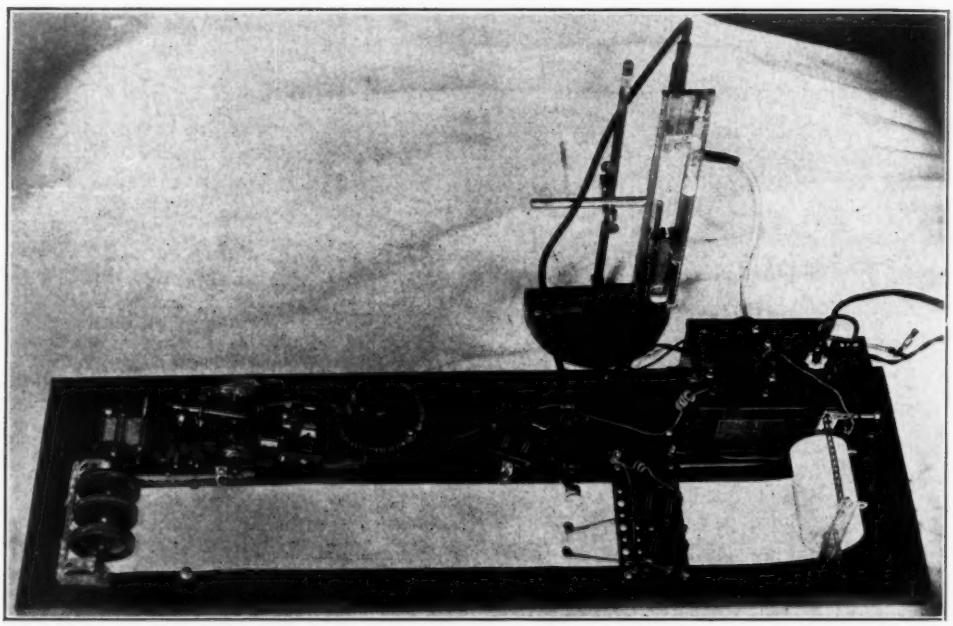

Fig. 3.—The kymograph assembled. At the left are the propelling wheels. Notice that the paper is curved around them. Above are the gear box and motor with rheostat. The connection between the mercury manometer and syringe used as recorder is shown. At the right is the transformer and electric clock.

The wheels are fixed between bearings to a length of shaft which extends into the gear box of the "Erector" set. The gear box affords a quadruple reduction of speed including a worm gear, but this is not enough for the purpose. In the present set the motor of an automobile windshield wiper has been used which contains an additional triple reduction within itself, and is operated by a transformer. A small motor with a worm gear reduction incorporated in it, such as may be obtained from laboratory supply dealers, would be preferable. Some sort of rheostat speed control is essential.

The transformer in the present set is also used to operate the signal magnets. There are three of these: one in shunt with the "Autopulse" pump, one to mark time, and one to record the application of stimuli, administra-

tion of drugs and the like. They are made from ordinary electric bells (of the best grade) with the bell, knob, cover and stamped base removed. For writing points, the smallest sized Keuffel and Esser lettering pen tips are used. The shank is bent into a sleeve to fit the vibrator of the bell. These writing points should be washed after use and kept in alcohol to prevent corrosion. If it were desired to eliminate the transformer, the signals could be operated from the storage battery with appropriate resistance interposed.

The timer is made of an electric clock with a sweep second hand. The best method of converting it to scientific purposes varies with the model of clock, but platinum contact points should be used in any case. In the present device an interval of fifteen seconds is convenient.

Blood pressure is recorded continuously from a mercury manometer connected by a T-tube to the intake of the pump and the femoral arteries. A thick-walled rubber tube passes from the distal end of the mercury manometer to the tip of a 5 c.c. syringe. The space between the top of the mercury column and the piston of the syringe is filled with 50 per cent glycerine, and the plunger of the syringe is oiled. Any movement of the column of mercury is transmitted to the piston of the syringe but the resulting excursion is inversely proportional to the squares of the radii of the two tubes respectively. The syringe is fastened horizontally at the edge of the strip of paper and a writing point secured to the piston. It is possible to obtain tracings of individual pulse beats by this arrangement, although of course on a reduced scale.

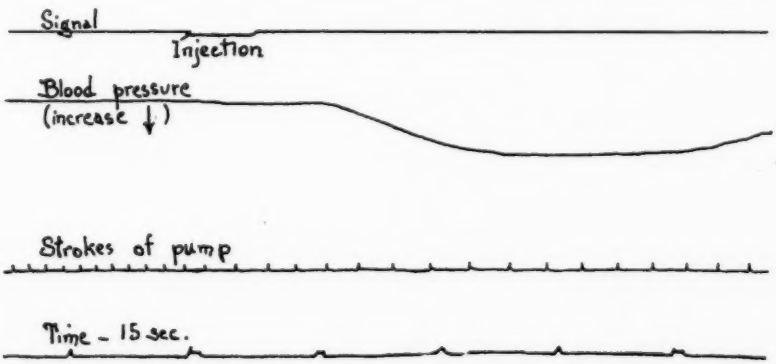

Fig. 4.—Sample of record. Perfusion of cat's common carotid under amytal. Effect of injection of 1/10,000 adrenalin into carotid: increase of blood pressure, slowing of strokes of pump.

The advantages of this kymograph are that it is inexpensive, portable, and compact. The timing device is self-contained. Records may be taken continuously over several hours and will show several signals simultaneously as well as recording blood pressure. Annotations may be made directly on the paper at the time they occur obviating the inconvenience of a separate set of notes.

A PIPETTE WASHING DEVICE*

THOMAS P. NASH, JR., PH.D., AND WILLIAM KRAUSS, M.D., MEMPHIS, TENN.

THE washing of the numerous pipettes required in the routine and research work of biologic laboratories is a vexatious and time-consuming detail. For a number of years we have employed for this purpose, and with much satisfaction, the device illustrated in Fig. 1.

The essential feature of the apparatus is the brass nipples threaded into lines of ⅜-inch or ½-inch brass pipe. Brass rod of ¼-inch diameter is cut

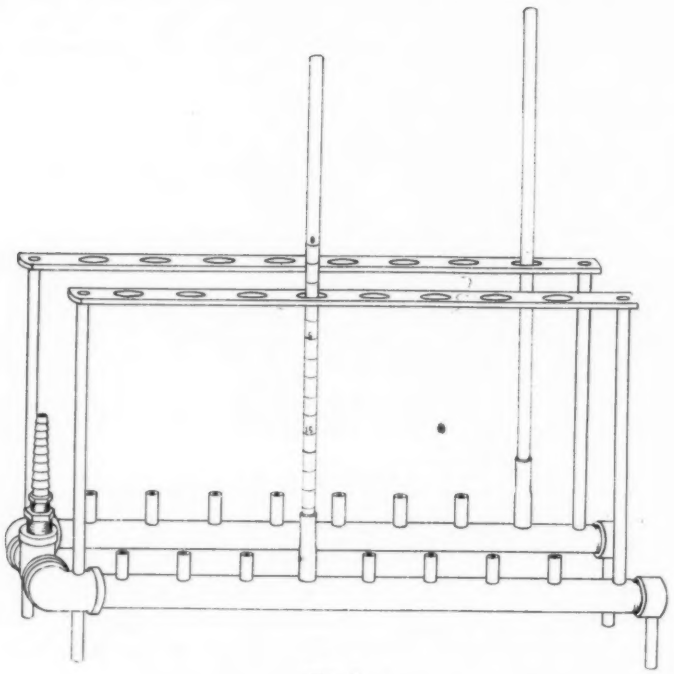

Fig. 1.

into ¾-inch lengths. These are threaded at one end and drilled from the opposite end with a ⅛-inch drill, the final 2 or 3 mm. at the threaded end being drilled through with a 1/32-inch drill. When these nipples are screwed into water lines the small diameter of the bottom openings suffices to maintain sufficient pressure in the system to force water through the tallest pipette even though only one pipette may be in the apparatus. The nipples are fitted with short lengths of rubber tubing which receive the tips of the inserted pipettes. In Fig. 1 only two of the nipples are shown with rubber connections

*From the Departments of Chemistry and Medicine, College of Medicine, University of Tennessee.

Received for publication, December 2, 1932.

and holding pipettes. Some suitable support, such as that illustrated, must be provided for the upper portion of the pipette. Only a moment's time is required to insert a pipette, and washing with constantly changing water then continues automatically until the pipette is removed.

The apparatus pictured is designed to be connected by rubber hose to a water cock, and may be moved from one sink to another. In our laboratories we have found it convenient to have a single line of nipples permanently installed near the bottom and at one end of each sink where the device interferes least with other uses of the sink.

A surprisingly large number of nipples may be assembled in a single unit without loss of efficiency. Since, however, water escapes from every outlet whether or not these are occupied by pipettes, a larger capacity unit than normally sufficient leads to an unnecessary wastage of water.

Test tubes, centrifuge tubes, and other similar pieces are conveniently and automatically washed in this apparatus by inverting them over glass tubes connected to the nipples.

THE CALIBRATION OF WHITE BLOOD CELL DILUTION PIPETTES*

F. LOWELL DUNN, S.B., M.A., M.D., OMAHA, NEB.

THE technical skill required in the manufacture of blood cell dilution pipettes must excite the admiration of all who give thought to the problem. Obviously such micro pipettes must show variations in precision. This fact is recognized by the manufacturers, some of whom provide factory certificates and guarantees of accuracy or individual certification either by themselves or by the Bureau of Standards. Textbooks of clinical pathology show a widely varied response to the possibility of pipette errors. At the one extreme is the statement that only pipettes certified by the Bureau of Standards should be used in clinical laboratories, while at the other extreme is the complete omission of any comment regarding the possibility of such errors. Probably the majority of physicians assume dilution pipettes as purchased to be sufficiently accurate for clinical purposes, or check them against other pipettes to maintain uniformity. Using the same pipette for consecutive blood counts on the same patient is a common device for ascertaining relative changes in leucocyte counts. This is a tacit admission of error in apparatus and is at best an inconvenient method in laboratories where a large number of pipettes are in daily use.

The extra charge made for reliable certification seems most reasonable to anyone who has undertaken such calibration. There is, however, a general impression among clinicians and hospital administrators that such certification is warranted only for purposes of academic research.

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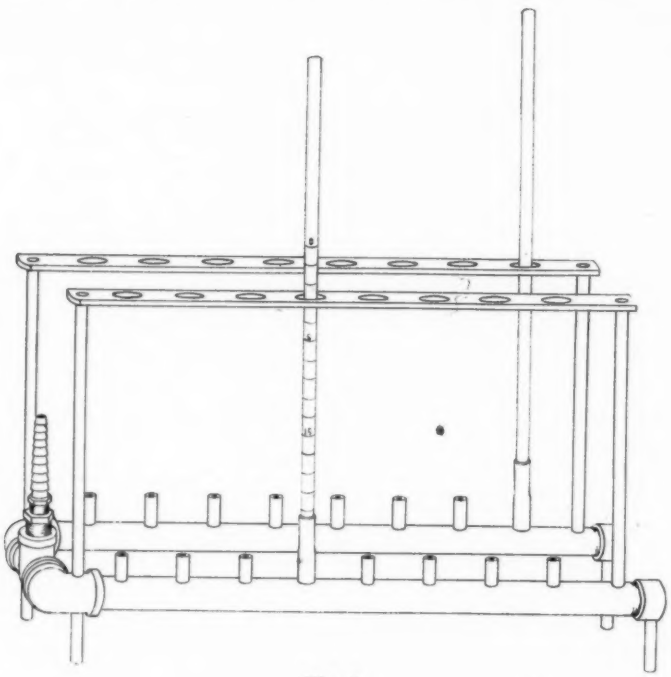

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F. Lowell Dunn, S.B., M.A., M.D., Omaha, Neb.

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The Bureau of Standards specifications for dilution pipettes with a 1 to 10 ratio require (in addition to certain details of construction) that the dilution must not be in error by more than ±3.5 per cent. This is, of course, the pipette error alone and does not include other possible sources of error such as, (1) technical manipulation of pipette and hemocytometer, (2) physiologic variations, and (3) errors in the construction of the hemocytometer. Since rises in leucocyte counts of 1000 to 2000 per cubic millimeter are often determining factors in formulating opinions regarding treatment, a method error of 10 per cent looms large and an error of ±3.5 per cent in the pipette alone is a large fraction of this total error.

The accidental discovery of a defective pipette in our own service raised the question of the accuracy of dilution pipettes in current clinical use. New lots of pipettes were supposed to be checked against older lots for consistency but this had been neglected because of lack of time. We were unable to obtain any impartial information and the discrepancy in textbooks of clinical pathology made it desirable to determine whether the extra cost of calibration was a justifiable expenditure. Through the courtesy of several physicians we obtained for calibration 86 white cell dilution pipettes.

METHODS

After inspection the pipettes were rinsed with nitric acid, bichromate cleaning mixture, water, alcohol, and ether until examination showed them to be clean.

Gravimetric.—The weights of distilled water or 1 per cent fuchsin included between the tip and the "0.5" mark, and between the tip and the "11" mark were determined. The necessary precautions in calibration of volumetric ware were observed.

This method was slow and since the weight of water included between the tip and the "0.5" mark was often not over 10 mg. it was necessary that the manipulations required in filling the pipette and the weighing itself must not introduce errors of over 0.1 mg. to determine the pipette error within 1 per cent. The necessity for technical skill and experience was shown by the amount of practice required before consistent results could be obtained, probably making this method available only to those who had survived the equivalent of an elementary course in quantitative analysis.

Peffer Method.—A much more promising method was that of E. L. Peffer of the Bureau of Standards.[1] His excellent instrument eliminates the handling of the pipettes during the calibration, requires considerably less skill, and is five to ten times faster than the gravimetric method. To construct a duplicate of his fine instrument was prohibitive, but it was obvious from his description that the basic features could be satisfied at a negligible cost.

The device, as assembled by us, is illustrated in Fig. 1 with the protective cotton cover removed. It consists of a small reservoir containing 1 per cent fuchsin, a one hole rubber stopper to fit the bulb end of the pipette, and a piston by which the fuchsin can be forced up into the pipette, the volume of liquid being measured by a micrometer screw feed on the piston. The pipette is placed vertically in the stopper, with the tip up. The solution is forced to the "11" mark and a reading is taken. It is then forced up to the "0.5" mark and to the tip, readings being made at each level. The result is a measurement of the desired volumes of the pipette in terms of micrometer screw piston displacements from which the dilution value of the pipette can be quickly calculated. The small reservoir in our apparatus was a Pyrex tee. A Brown and Sharpe micrometer head was cemented into one end of the tee with De Khotinsky cement. The other end was closed with cement. The tee was used in order to secure rigid clamping to the ring stand by the usual laboratory supports. The upright portion of the tee was fitted with a rubber stopper. A single hole was bored,

the size being selected to fit tightly the bulb ends of the pipettes to be calibrated. The inner end of the rubber stopper was made concave so that air bubbles would not be trapped, but could be forced out through the hole in the stopper. The system was then filled with 1 per cent fuchsin and all air bubbles carefully expelled.

Slight fluctuations of temperature of the fuchsin solution produce marked variations in the height of the solution in the capillary tube of the pipette. Consequently the apparatus must be carefully shielded. Peffer shielded his apparatus by a vacuum container. We wrapped the tee with several layers of cloth before clamping it to the ring stand, and then surrounded tee, clamps, and part of the ring stand with cotton, leaving only the rubber cork and the micrometer head exposed. The cotton was put on in layers to a thickness of two to four inches, being careful that all air channels were closed. The knurled portion of the micrometer head was covered with several wrappings of cloth to protect it from the heat of the hand. This protection was sufficient if drafts were avoided, although on a few days

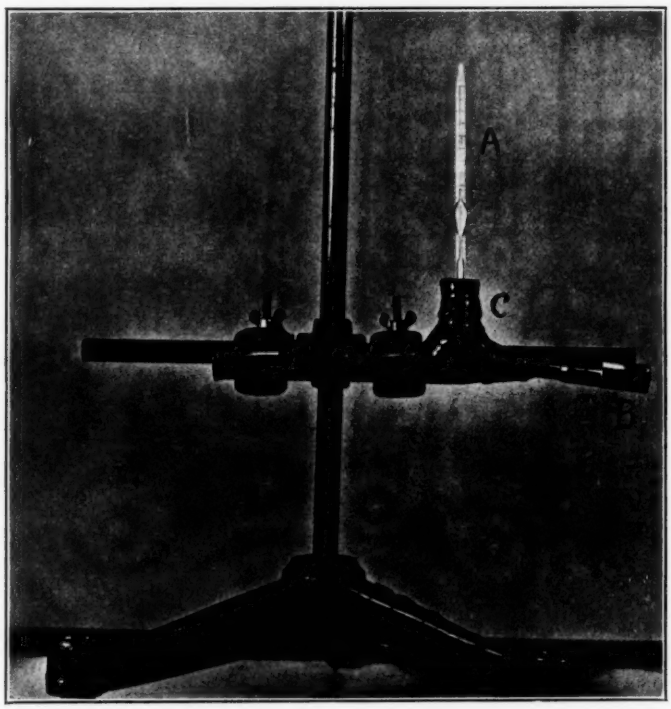

Fig. 1.—Dilution pipette calibrator for white blood cell pipettes utilizing some of the features of Peffer's instrument. *A*, white pipette; *B*, micrometer head; *C*, tee reservoir. The cotton cover to minimize thermal effects has been removed.

temperature fluctuations made consistent readings impossible. Later, by partly filling the tee with hard paraffin, the volume of liquid was reduced from about 30 c.c. to 8 c.c. and the temperature effect was definitely less marked.

Several practical details developed during use. The rubber stopper should fit the tee and the pipette tightly and without any tendency to crawl. It was preferable to cement the stopper to the tee. Any crawl was apparent in duplicate readings, or the shift in the fluid level could be observed after waiting a minute or two. The crawl could be accelerated by gently tapping the pipette with a pencil. After setting the level at the "11" mark, it proved useful to tap the pipette to minimize any crawl during the subsequent readings. Bubbles occasionally adhered to the glass bead in the bulb of the pipette. These should be watched for very carefully during the filling of the bulb and should be removed by tapping.

Any air in the system caused erratic results and lag in response when the piston was moved. This was due to incomplete filling of the reservoir or to failure in keeping the

hole in the stopper sufficiently filled with fuchsin. The reservoir was kept filled by dropping the fuchsin solution on the stopper and drawing it in by means of the micrometer screw. The pipettes must of course be dry for each set of measurements, although measurements of the interval between the tip and the "0.5" mark could be duplicated usually without drying between determinations.

The meniscus should be set flat across the orifice when the setting at the tip is made. Many pipettes show a constriction in bore at the tip, and it is our experience that lag due to small amounts of air show up most conspicuously in this region. The setting at the tip is best made with the aid of a magnifying glass.

The method described above proved much more satisfactory than the gravimetric. If the reservoir is so designed that air bubbles are not trapped, the system is easily filled. Skill in attaching the pipettes is quickly acquired, and it is easy to control accurately the level of the solution by the micrometer screw. This method measures the pipette error directly and does not include the errors of filling and handling the pipette as in the gravimetric method.

Colorimetric Method.—The dilution value of the pipette can be measured directly in a colorimeter against a standard dilution. Several colored solutions were tried and 20 to 30 per cent chromic sulphate was selected because of the high sensitivity of the eye for green and because twenty-two fold dilution still gave a satisfactory intensity in the colorimeter at a cell depth of 20 mm. The standard dilution was a 1:22 dilution of the strong solution. The concentrated chromic sulphate solution was sucked up to the "0.5" mark and then diluted to the "11" mark with distilled water. After shaking a moment the entire contents were discharged into a colorimeter cup. This process was repeated, drying the pipette each filling until sufficient solution was obtained to give an effective depth of 20 mm. With microcolorimeter cups one to three fillings were sufficient, the larger all-glass cups requiring four or more fillings. This might appear to be a drawback in the method, but it is compensated by the fact that the colorimeter reading is an average of several fillings.

The evaporation of the liquid in a glass microcolorimeter cup was measured and found to be about one milligram in fifteen minutes at 27° C. on a dry day when the cup was covered with a watch glass. Since the total volume of leucocyte pipettes is usually 0.25 c.c. or more, this loss is not significant. Furthermore with a suitable suction pump and the use of alcohol and ether the pipettes can be cleaned and dried in a minute or two so that three fillings and the necessary cleanings can be accomplished within ten minutes. A 30 per cent chromic sulphate solution was tested for change of color over the temperature range of 24 to 45° C. None was observed.

The green color can be very satisfactorily matched in the colorimeter, but faulty use of such instruments is so common that several details should be mentioned. The zero settings should be carefully checked. The colorimeter should be symmetrically placed with respect to the illumination. Any inequality in the fields should be located and rectified and not compensated by twisting the position of the instrument with respect to the light. If the plungers are not dry, they can be rinsed with the standard solution since it closely approximates the strength of the unknown. When a series of pipettes are to be calibrated, the standard solution should be changed frequently enough to avoid appreciable evaporation. The colorimeter light should be turned off when readings are not being made.

This colorimetric method appeared to us logical and was much easier to do than the difficult gravimetric method. Colorimetric methods are more familiar to the clinical laboratory worker than gravimetric. The hydrometric method of Peffer is perhaps not so applicable to general use because of this drawback of unfamiliarity. The colorimeter method showed no greater variation in our hands than those obtained with the use of our makeshift micrometer screw calibrator. With the increase in ruggedness and precision of photoelectric circuits the adaptation of the colorimetric method to a photoelectric one is an obvious technical procedure. Since the colorimetric readings for certifiable pipettes are within ±3.5 per cent, it might

prove unnecessary to use a photometric head, the readings being made by galvanometer deflection. The speed of such a device should materially reduce the cost of pipette calibration.

The calibration of the various pipettes was controlled by: (1) repeated checks on different days, (2) check against the gravimetric method, and (3) comparison with the Bureau of Standards certified pipettes. Three or more readings were averaged. Most of the readings were made with the micrometer screw calibrator.

DISCUSSION

A few of the pipettes were discarded because of tips broken sufficiently to affect the accuracy, leaving a total of 84 to be discussed. Of these 10 bore no visible identification mark while the rest included 13 different distributors' names or identification marks. All but 18 had a serial number. We do not know how many manufacturers were represented in this series of 84 pipettes, but we are informed that the manufacture of these pipettes is a highly specialized industry and confined to very few firms. Only one pipette

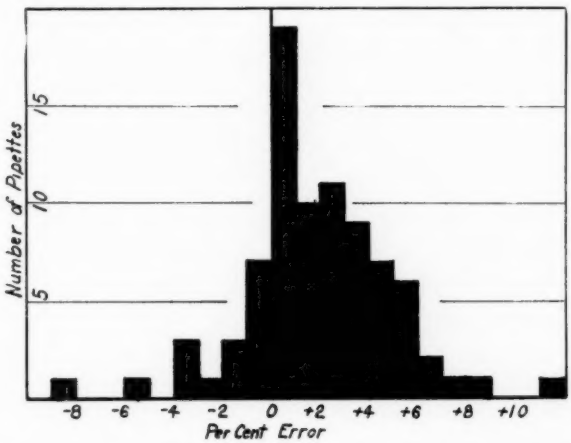

Fig. 2.—Frequency curve of errors of 84 white blood cell dilution pipettes.

had been recognized as being in error prior to our calibrations. One pipette, not included in the series, had no mark whatever on the capillary stem. We were unable to associate defective pipettes with any particular identification mark. It was possible to obtain catalogue specifications, guarantee, or factory certificates on 63 pipettes. The small size of our series does not permit in any sense a general statement but with this qualification the nature of the guarantee or specification had little or no bearing on the accuracy of the pipette except in those cases where there was an explicit statement that the pipette had been individually calibrated. All pipettes that had been individually calibrated were within the tolerance stated. Under present conditions the inference can be tentatively made that individual calibration is necessary to eliminate defective pipettes.

The results of our calibrations were plotted in a frequency curve to conserve space (Fig. 2). Of the 84 tested, 24 (28 per cent) showed errors in excess of ±3.5 per cent. Of these, 10 (11.5 per cent) were in the group 3.5 to 5 per cent, 12 (14 per cent) in the group of 5 to 10 per cent, and 2 were over

10 per cent, one of which had an error of 38 per cent. It is interesting that plus errors were more common than minus errors and in the ratio of 68 to 16. Since a portion of the calibrations were done both by the micrometer screw piston method and by the colorimetric method we were unable to explain the frequency of the positive errors on the basis of the method of calibration.

With 28 per cent of the pipettes showing errors in excess of ±3.5 per cent, the possibility of serious errors arising in laboratories where a large number of pipettes are in use is far from negligible even for clinical purposes.

SUMMARY

1. Calibration of 84 white blood cell dilution pipettes in clinical use showed 28 per cent to have errors in excess of ±3.5 per cent, 11.5 per cent to have errors of 3.5 to 5 per cent, and 14 per cent to have errors of 5 to 10 per cent with two having errors of 11 per cent and 38 per cent respectively.

2. Positive errors were more common than negative in the ratio of 68 to 16.

3. A colorimetric method for the calibration of dilution pipettes has been described.

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DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

PERTUSSIS, Production of Antipertussis Serum of High Titer, Bailey, J. H. J. Infect. Dis. **52**: 97, 1933.

By repeated intraperitoneal injections into cocks of massive doses of a suspension of live, virulent pertussis bacilli, an antipertussis serum of high titer, not causing serum sickness even in large doses, was produced, which, in the limited trial afforded it, gave evidence of being of value in the treatment of pertussis in children. No definite statement as to the therapeutic value of this serum may be made until a greater number of patients have been treated.

SYPHILIS, Serodiagnosis of, Denison, G. A., and McDonald, E. G. Am. J. Syph. **17**: 90, 1933.

Serologic tests for syphilis because of their complicated and empiric nature are subject to variation, and the use of standardized technics in different laboratories does not mean that comparable results will be obtained. Each clinician should have a very definite idea of the clinical level of the tests performed for him. Clinician and serologist should work together, each sympathetic of the other's problems.

Various tables are compiled showing comparative results obtained with several methods as used in a board of health laboratory. However, it should be emphasized that similar results would not necessarily follow in other laboratories using the same methods. For this reason only very generalized deductions should be made.

A close comparison of methods cannot be made by tabulating results on all specimens from cases of a general nature since the large number of negative routine examinations minimize the differences. True comparisons are best made on treated and untreated syphilitic cases. Finally, where results disagree a close check of clinical findings should be made to determine the correlation. Judged in this way the apparent working agreement of 93.6 per cent obtained on all specimens with four antigenic tests is reduced to 89.1 per cent in untreated and 79.5 per cent in treated syphilis. The greatest number of disagreements occur in recently treated cases. However, there are always a small number of syphilitic cases which for some reason are positive only with one method or another.

The authors' experience justifies the conclusion that no single test is ideal for confirmatory diagnosis and treatment of syphilis, that none of the technics studied have any inherent specific qualities, and that the best results may be expected from the use of multiple tests which include at least one precipitation and one complement fixation method. The authors believe that multiple tests allow greater latitude in the quantitative estimate of the patient's serology, and, thereby, serve as a better guide for treatment.

PNEUMONIA, Specific Serum Treatment of Type I, Parsons, J. W., and Sutcliff, W. D. Am. J. M. Sc. **186**: 52, 1933.

The effectiveness of two methods of dosage of specific serum in the therapy of pneumococcic Type I lobar pneumonia is compared in two groups of 12 cases each, treated before the fifth day of their disease. In the first group amounts of serum were given (15 to 105 c.c., average 45 c.c.), just sufficient to maintain agglutinins in the circulating blood, as determined by a rapid bedside method. In the second group a larger, empirically selected dose (75 c.c. or more, average 79 c.c.) was given to each patient.

In both groups the response to the therapy was satisfactory as shown by the short duration of the disease after therapy, and by the death rate. On the average, the course of the disease in the 12 empirically treated patients was much shorter than the average course of a larger series of cases treated in the same manner, but this unusual result in a small series of cases does not necessarily indicate the superiority of this method of therapy.

Evidence is given to indicate that the persistence of agglutinins for the hemologous organism is an index that a sufficient amount of antipneumococcic serum has been administered to produce a satisfactory therapeutic result.

TUBERCULOSIS: The Question of Tubercle Bacilli in the Blood in Advanced Pulmonary Tuberculosis, Corper, H. J., and Damerow, A. P. Am. Rev. Tub. **28**: 118, 1933.

Tubercle bacilli were not found to be present in the blood of 120 patients with advanced pulmonary and generalized tuberculosis at the National Jewish Hospital and Fitzsimons General Hospital at Denver, Colorado, in spite of the fact that each blood specimen was submitted to four different methods of examination for tubercle bacilli, namely, guinea pig inoculation, and three different culture methods. While control tests proved the efficacy of the culture methods used for discerning small numbers of tubercle bacilli in human and animal blood, acetic acid, as recommended by Loewenstein, destroyed small numbers of human tubercle bacilli, while saprophytic acid-fast bacilli would survive such treatment, thus vitiating the results obtained with this reagent.

In addition to the 120 cases studied, over 200 routine smaller specimens of blood obtained from patients in a tuberculosis sanitorium and examined by means of two reliable culture methods, the tissue-substrate method and the sulphuric acid crystal violet potato cylinder method, did not reveal a single positive culture for tubercle bacilli among these specimens. As a result of the examination of the blood from the 120 cases of advanced tuberculosis two specimens yielded saprophytic acid-fast bacilli, which could readily be differentiated from pathogenic tubercle bacilli by animal inoculation and reliable culture methods.

Tubercle bacilli were found to grow well when present in small numbers on a sulphuric acid treated and sodium bicarbonate or sodium hydroxide neutralized blood residue or on inspissated defibrinated blood, making it appear that the acid- or heat-treated or sterilized blood pigments are not detrimental to the growth of tubercle bacilli. The macroscopic type of culture obtained on the blood medium differs from that seen on potato or on egg, which also differ from each other.

The Congo red potato flour egg medium (Loewenstein) is a good one for human and bovine tubercle bacilli, but it is no better than a simple potato cylinder or inspissated egg yolk medium, and it possesses the disadvantage of being unnecessarily encumbered with expensive and unessential ingredients.

It appears that human or bovine tuberculobacteremias, in the sense that tubercle bacilli circulate in the blood for a fairly long time or that the bacilli multiply in the blood, are not borne out by these studies, although it is not intended to convey the impression that occasional embolic disseminations (showers) from disintegrating tuberculous foci do not occur or that there may not exist terminal periods in the course of the disease when numerous showers of caseous products containing viable bacilli may make it possible to find them in the blood of man and experimental animals. However, such a condition of tubercle bacilli in the blood is far from being the common event, according to the observations made in this study.

It would appear also that embolic showers (embolemia), when they do occur in man, are rapidly removed from the circulation in the usual case of tuberculosis.

DIPHTHERIA: Active Immunization Against, by a Single Injection, Strauss, H. W. J. A. M. A. **101**: 192, 1933.

A concentrated diphtheria toxoid incorporated in hydrous wool fat has been injected intramuscularly and actively immunized 99 per cent of 103 patients within a period of two

months. In the majority of cases, immunity developed in from three to four weeks and, in one case, as early as two weeks.

Because of the early development of active immunity, a preparation such as that described may have a practical usefulness in checking an epidemic of the disease. A single injection method has obvious practical advantages.

The material used in this study was prepared in the following manner: Diphtheria toxoid (M.L.D. 500 per c.c.; L. 0.13; L.F. 0.1), 7,300 c.c. was placed in cellophane bags and fanned at room temperature until the volume was reduced to 250 c.c. The dark colored granular precipitate that formed was removed by centrifugation. The supernatant fluid was diluted up to 730 c.c. in the process of twenty-four-hour dialysis in a cellophane sack and by the addition of distilled water. Phenol (0.5 per cent) was added and the solution was filtered through a Berkefeld candle. The least fatal dose of the concentrated solution was 0.014.

In a similar way, the solution was further concentrated to 73 c.c. (100:1 concentration). This was preserved, after Berkefeld filtration, with merthiolate in a final concentration of 1:10,000. This concentrated fluid was found to contain 300 flocculating units per cubic centimeter.

Two batches of the lanolin mixture were prepared as follows: Batch 301-H-11 was made by thoroughly mixing, at 42 C., 100 c.c. of sterile hydrous wool fat and 50 c.c. of concentrated diphtheria toxoid. One cubic centimeter of this mixture thus contained 100 flocculating units and 0.2 c.c. contained 20 flocculating units. Batch 301-H-12 was made in the same way as 301-H-11 with the exception that, to each quantity of 0.2 c.c. of the mixture, 0.05 c.c. of sterile olive oil was added.

The material was received in individual miniature antitoxin syringes, each containing a single dose. The preparation is of the consistency of a soft wax and is easily expelled from the syringe.

No reactions were observed in children under five years of age. In the school age group there was an occasional complaint of soreness in the arm for a day or two with slight local redness and in one case a temperature of 101 during the first twenty-four hours. In the adult group, five who had positive Schick but negative control reactions were included in the series. They complained only of a heavy feeling in the arm. Five other adults (not included in the series) who gave positive Schick and control tests were given the injection. Of these, two gave severe reactions with a rise of temperature to 102, headache, malaise, a large area of local redness with induration, and regional adenitis. The fever subsided in twenty-four hours. The three remaining persons had mild local reactions without constitutional symptoms. The reactions to be expected, then, are the same as those obtained with ordinary toxoid. They are infrequent and quite mild in older children and absent in those of preschool age. The more severe reactions are to be expected in those patients who give positive reactions to both Schick and heated control material.

PERTUSSIS: Occurrence of the Bordet-Gengou Bacillus, Kristensen, B. J. A. M. A. **101:** 204, 1933.

The results of this study are conformable with the hypothesis that the Bordet-Gengou bacillus is the etiologic agent of whooping cough.

The cough-plate method has been used for sixteen years at the State Serum Institute in Copenhagen and has proved to be of practical value. It is the best method for diagnosing the disease early.

An isolation period of four weeks after the onset of the typical paroxysm has in practice been sufficient for school children.

Healthy carriers have not been found outside of families in which whooping cough exists.

Abortive and quite atypical cases of whooping cough are frequently found, and the author believes they play an important rôle in the spread of the disease.

PUERPERAL INFECTION: Relationship Between Exogenous Throat Streptococci and, Kellogg, F. S., and Hertig, A. T. Trans. Am. Assn. Obst. Gynec. & Abd. Surg. 87: 1932.

From a study of an epidemic in the maternity wing of a well-equipped general hospital in 1931, it is concluded:

That nasopharyngeal carriers of hemolytic streptococci (and perhaps other organisms) are a most dangerous source of frequently fatal sepsis to women in childbirth from the moment labor begins (and possibly before), to the end of the puerperium (at present an unassignable date but at least fourteen days after delivery).

That "silent carriers" are potentially as dangerous as persons acutely sick with temperatures, save for less likelihood of coughing or sneezing, although, usually, a history of some acute exacerbation in the not distant past may be obtained from the carrier.

That perineal contacts are presumably the most frequent method of transmission; either by coughing, sneezing or talking with the patient during perineal precautions or by incomplete manual asepsis after self-infection of the hands by the carrier, as by the use of a handkerchief; but that for the present other less direct methods must be assumed, and guarded against.

Hence, that every carrier is a source of danger and must be eliminated or be masked adequately at all stages of labor and the puerperium and be absolutely trained and trustworthy about digital asepsis.

That since pupil nurses are untrained and unhabited to conscientious digital asepsis, it is a wise precaution to culture each one on entrance to a maternity hospital and to eliminate each one temporarily until the throat is negative for hemolytic streptococci.

That other personnel, i.e., doctors and graduate nurses trained in asepsis, following rules akin to those given above, will in all probability not prove a hazard to patients.

That the question of ward attendants, especially those serving food, must be carefully considered.

That a single case of puerperal sepsis in an institution calls for immediate rigid investigation and drastic measures based on this to limit spread.

MILK: The Use of Glycerol as a Preservative for Specimens to Be Examined for Hemolytic Streptococci, Gilbert, R., and Clark, M. E. Am. J. Pub. Health 23: 720, 1933.

The addition of glycerol to make a 30 per cent concentration has been found to enable recovery of streptococci from milk after seven days at room temperature or after ten days' refrigeration. It is thus of value in the study of epidemics of septic sore throat.

THYROID DISEASE: Effect of Treatment on Blood Cholesterol in, Hurxthal, L. M. Arch. Int. Med. 521: 86, 1933.

The blood cholesterol is low in toxic thyroid states, and is brought to a normal level partly by preoperative treatment but chiefly by subtotal thyroidectomy.

The reciprocal relationship between the average elevation of the basal metabolic rate and the average lowering of the blood cholesterol level in toxic goiter, is further confirmed by the results of treatment presented in this paper.

There appears to be little difference between the change in the blood cholesterol values in exophthalmic goiter and that in toxic adenomatous goiter as the result of treatment.

The blood cholesterol in nontoxic adenoma or adenomatous goiter undergoes little or no change as the result of removal of the growth.

The blood cholesterol determination is of distinct but limited value in the diagnosis of hyperthyroidism.

BLOOD CULTURES: Comparative Study of, Taken With Kendall and Routine Mediums. Friedberg, C. K. Arch. Int. Med. **52:** 120, 1933.

One hundred and three routine blood cultures were made for 77 patients suffering from a variety of febrile illnesses suggesting the presence of bacteremia. Simultaneously, flasks containing K medium were inoculated with blood from these patients.

The K medium showed 4 per cent less positive results than the ordinary routine method. Compared with the individual flasks and plates used in the ordinary method, the flask of K medium showed slight inferiority to some and slight superiority to other individual units.

Other disadvantages were found in the difficulty and expense of preparing the medium and the greater time necessary before an organism could be identified.

Repeated subcultures from the original K flask failed to show any invisible, filterable forms which could be converted to the ordinary state by transfer to solid medium as alleged by Kendall. There was no evidence in the cases studied to show that the clinical picture was due to a filtrable, invisible form of an organism which did not show itself on the ordinary mediums.

In several instances common organisms were found to pass through the Berkefeld filter, suggesting the possibility that the K medium may have had some influence in impairing the efficiency of the filter.

LIVER FUNCTION: An Appraisal of the Modified Dextrose Tolerance Tests, Ricketts, H. J. Arch. Int. Med. **52:** 147, 1933.

The test in question follows:

1. Estimation of blood sugar during fasting was made in the morning.
2. The patient was then given 20 units of insulin.
3. Twenty minutes later, the patient was given 50 gm. of dextrose in 500 c.c. of water by mouth, followed by 1,000 c.c. of water by mouth.
4. Blood sugar determinations were made at one-half hour, one hour, two hours and three hours after the ingestion of the dextrose and water.

The modified dextrose tolerance test of the function of the liver, as described by Althausen, Gunther, Lagen and Kerr, was performed on ten patients who were considered to have normal livers at the time of examination, and on four patients with frank hepatic disease.

Of the ten normal patients, nine responded to the test by a drop in blood sugar to points considerably below the critical level for normal reactions, and showed symptoms and signs of hypoglycemia.

Of the four patients with frank hepatic disease, three responded by definite chemical and clinical hypoglycemia.

There was no essential difference between the behavior of the normal and the abnormal groups.

The modified dextrose tolerance test in its present form is not a satisfactory measure of the metabolic function of the liver.

PREGNANCY, Hormone Diagnosis of Viability of, Spielman, F., Goldberger, M. A., and Frank, R. T. J. A. M. A. **101:** 266, 1933.

Thirty-three pregnancy cases in which missed abortion was suspected or expected were studied from the hormonal aspect in order to determine the relationship between the female sex hormone of the blood and the pituitary hormone of the urine on the one hand, and fetal life or death on the other.

The Frank-Goldberger method was used in the blood studies, and either the Aschheim-Zondek or the Friedman test in the urine studies.

A negative female sex hormone reaction was obtained when the fetus was dead (23 cases) and a positive reaction when the fetus was alive (8 cases). The results here were 100 per cent correct.

A negative pregnancy reaction was obtained when the fetus was dead in eleven cases, and ten cases gave positive reactions in spite of dead fetuses (approximately 50 per cent correct).

The female sex hormone blood determination has proved itself in this small series an absolute indicator of whether a fetus is alive or dead. The urine pregnancy test is of value only when the reaction is negative.

The presence or absence of the hormones depends on the degree of involution of the placenta and its attachment to the uterine wall.

TUBERCULOSIS: The Tuberculin Patch Test, Grozin, M. Am. J. Dis. Child. **46:** 17, 1933.

The tuberculin patch test is made by moistening a piece of adhesive plaster with 1 or 2 drops of tuberculin and applying it to the skin, which has previously been cleaned with ether. For control, a piece of adhesive plaster without tuberculin may be used. A positive reaction is indicated by redness studded with papules and vesicles.

A study of 176 cases showed that this method compared favorably with the Pirquet test as to reliability.

Its advantages over the Pirquet test and other tuberculin tests are:

a. It is absolutely painless and therefore does not spoil the relation between child and physician, or frighten a neurotic patient or anxious mother.

b. It requires no boring, puncturing, scratching or rubbing.

c. It requires no sterilization of instruments, such as lancets, needles, and syringes.

d. There is no danger of infection.

e. It is of much simpler technic, so that it can be done by nurses without much training.

f. It is less time-consuming, since there is no waiting for the tuberculin to dry or to act on the skin, or watching that the child does not wipe it off or spread it to the area of control. It is therefore of advantage when large numbers are to be tested or in busy practice.

g. It is possible to control the area of reaction, since this is usually limited to the surface covered by the adhesive plaster. In other percutaneous tests, such as the Moro, the reaction cannot be controlled, once it has started, because the tuberculin must be rubbed into the skin, and friction of clothes tends to spread it still further. In the tuberculin patch test the reaction can be regulated by the size of the adhesive plaster, by the number of drops of tuberculin and by the strength of the dilution.

h. It is easier to interpret the results with the tuberculin patch test, because the area of reaction can be arbitrarily enlarged by applying larger pieces of adhesive plaster, more tuberculin and tuberculin of greater concentration.

PNEUMONIA IN INFANTS, Due to B. Mucosus-Capsulatus, Jerguson, J. A., and Tower, A. A. Am. J. Dis. Child. **46:** 59, 1933.

Two cases of lobular pneumonia in infancy caused by *Bacillus mucosus-capsulatus* have been reported; the twins were seven months old, a girl and a boy. The girl contracted the disease first and died on the eighth day. The boy became ill two days after the onset of the illness in his sister but completely recovered after thirty-two days' hospitalization.

Bacteriologic examination of the throat and tracheal secretion is the most important procedure from a diagnostic standpoint. The extreme pallor of the skin and dehydration, the cough and mucopurulent nasal discharge in the two cases described in this report, together with the vomiting and diarrhea which cleared up early in the disease, are suggestive from a standpoint of differential diagnosis.

Pneumonia in infants due to *Bacillus mucosus-capsulatus* may not terminate fatally. The pulmonary involvement is, perhaps, most often lobular, and the roentgen signs which are characteristic of the disease in adults may not occur in infants.

HEMOGLOBIN, Content of Blood in Infants, Elvehyem, C. A., Peterson, W. H., and Mendenhall, D. R. Am. J. Dis. Child. 46: 105, 1933.

A hemoglobin curve for infants constructed from 2,000 determinations on 750 subjects varying in age from birth to five years is given.

The hemoglobin content of the blood of infants was found to be high (22 gm.) but it fell rapidly and reached a low point at the age of from eight to twelve weeks. There was an increase between the ages of twelve and twenty-four weeks, and a slight decrease thereafter. The hemoglobin remained between 11 and 12 gm. until the infants were about two and one-half years old, after which it increased gradually.

The rapid drop during the first few weeks of life and the low hemoglobin values recorded during the first six months were not prevented to any appreciable extent by the feeding of a good diet of natural foodstuffs. The hemoglobin values of the children on the special diet, however, began to increase at an earlier age than the average values for all the children.

REVIEWS

Books and Monographs for Review should be sent direct to the Editor, Dr. Warren T. Vaughan, Professional Building, Richmond, Va.

The Aetiology of Tuberculosis*

THIS is an English translation made by Dr. and Mrs. Max Pinner of Robert Koch's original communication on the etiology of tuberculosis which appeared in the *Berliner Klinische Wochenschrift* the tenth of April, 1882. The present volume was prepared by the National Tuberculosis Association to commemorate the fiftieth anniversary of the discovery of the cause of consumption. Dr. Allen Krause contributes an introductory appreciation of the epoch-making contribution of Koch. The booklet is illustrated with facsimiles of the first page of Koch's original paper and several other pertinent photographs.

Only two English translations have previously appeared, one in the *Canada Medical and Surgical Journal*, 1881, and the other in the *Cincinnati Lancet and Clinic*, 1883.

Koch's original contribution, long since a classic in medicine and an epoch-making paper, should long since have been available in this form and the translators and the Tuberculosis Association are to be congratulated.

Calcium Metabolism and Calcium Therapy†

AN EXHAUSTIVE and at the same time authoritative treatise on our knowledge of the metabolism of calcium and its use in the treatment of disease. While the major portion of the volume is given to those diseases in which there is a clear-cut error in calcium metabolism, the author also includes a discussion of quite a variety of diseases in which the use of calcium is certainly a moot question. The author of course recognizes this fact and outlines the treatment that has been recommended in this particular type of disease by those who claim to have obtained good results.

Outline of the Cranial Nerves‡

THIS is a small reference manual for students and for those of us who after a certain number of years find it difficult to recall the origin, distribution, functions, etc., of the cranial nerves. One of the author's innovations which appears to be especially logical is his process of tracing the sensory nerves from the sensory end organs backward centrally, rather than in the usual reverse. The motor organs he traces from the central point of origin of impulse to the periphery. One who has learned the cranial nerves with this method should be better able to keep them distinct in his mind.

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*The Aetiology of Tuberculosis. By Dr. Robert Koch. A translation from the German of the original paper announcing the discovery of the Tubercle Bacillus, read before the Physiological Society in Berlin, March 24, 1882, and published in the Berliner Klinische Wochenschrift, 1882, xix, 221, specially prepared for The American Review of Tuberculosis, March, 1932, by Dr. and Mrs. Max Pinner. With an introduction by Dr. Allen K. Krause. Cloth, pages 48. Published by the National Tuberculosis Association, New York, 1932.

†Calcium Metabolism and Calcium Therapy. By Abraham Cantarow, M.D. Instructor in Medicine, Jefferson Medical College; in charge of Laboratory of Biochemistry, Jefferson Hospital; Assistant Physician, Philadelphia General Hospital. With a Foreword by Hobart Amory Hare, B.Sc., M.D., LL.D. Late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia. Second Edition, thoroughly revised, 252 pages, illustrated, limp binding. Lea and Febiger, Philadelphia, 1933.

‡Outline of the Cranial Nerves. By John Favill, A.B., M.D., F.A.C.P. Associate Clinical Professor of Neurology, Rush Medical College of the University of Chicago. Cloth, pages 112. The University of Chicago Press, Chicago, Ill., 1933.

Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease*

ALTHOUGH diseases which are now attributed to the fuso-spirochetal symbiosis can be traced back in medical history even to the time of Hippocrates, our attention has been more centered on them since the World War following which the dissemination of trench mouth has forced our interest in the condition. This volume discusses the biologic and cultural characteristics of oral spirochetes and fusiform bacilli, their symbiosis, and the characteristics of related organisms. Following this there is a clinical discussion of the various forms in which the infection may manifest itself including disease of the oral cavity, the bronchi, the lungs, the eyes, ears, mastoid, the nose and sinuses, the esophagus, meninges, brain, intestines, appendix, skin, and genitalia. In each case clinical characteristics, laboratory identification and therapeutic methods are presented in all necessary detail.

There has been a need for a volume such as this and it may be well recommended.

Criteria for the Classification and Diagnosis of Heart Disease†

THIS small volume, edited by the Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, and approved by the American Heart Association, illustrates well the further application of the use of the *Standard Classified Nomenclature of Disease*, reviewed above. There will always be in the specialties need for a special system of classification of those maladies in which the physician is particularly interested. Both of these volumes have been approved by the American Heart Association and each finds its place. The volume under present review is that which would be of particular interest to those interested in cardiology. Its discussion of nomenclature in this particular field goes into much greater detail than the *Standard Nomenclature* but uses essentially the same system. In a large appendix we find very instructive chapters on radiologic diagnosis, involving orthodiagraphic tracings, and on diagnosis in the interpretation of electrocardiograms.

Outline of Preventive Medicine‡

TO MANY the title of this volume will be somewhat misleading insomuch as it suggests the public health aspects of the subject. The volume is, however, not written from this viewpoint but rather from that of individual preventive medicine. It is a treatise prepared under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine, to which 24 outstanding physicians of New York have contributed, and dealing with the early recognition and prevention of disease in the individual. Starting with a chapter on the principles and methods of the periodic health examination, it next presents a detailed discussion of the incidence of disease. There follows a section on laboratory aids in the early recognition of disease. Next comes a section on preclinical medicine and hygiene, emphasizing particularly the methods that should be applied with the individual patient in the prevention of possible future disease. Most of the remainder of the volume deals with those diseases of medicine, surgery and the specialties in which early recognition or prevention can

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*Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease. By David T. Smith, A.B., M.D. Association Professor of Medicine, Duke University, School of Medicine, Durham, N. C. Formerly Bacteriologist and Pathologist to the New York State Hospital for Incipient Tuberculosis, Ray Brook, N. Y. Cloth, pages 243. The Williams and Wilkins Company, Baltimore, 1932.

†Criteria for the Classification and Diagnosis of Heart Disease. By the Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, Inc., Joseph H. Bainton, M.D., Robert L. Levy, M.D., Arthur C. DeGraff, M.D., Harold E. B. Pardee, M.D., Chairman. Approved by the American Heart Association. Third Edition, cloth, pages 131. New York Tuberculosis and Health Association, New York, 1932.

‡Outline of Preventive Medicine. For Medical Practitioners and Students. Prepared under the auspices of The Committee on Public Health Relations, New York Academy of Medicine. 24 Contributors. Editorial Committee, Frederic E. Sondern, Chas. Gordon Heyd and E. H. L. Corwin. Second Edition revised and enlarged, cloth, pages 462. Paul B. Hoeber, Inc., New York, 1932.

be accomplished or in which treatment should be instituted at an early stage in order to prevent the ravages of the later stages. As one contributor writes, "every late case was at one time an early one."

The popularity with which this volume has been received is readily understandable.

Surgical Pathology*

THE third edition of Boyd's *Surgical Pathology* follows the general program laid out in the first two editions. While there is much on microscopic pathology, gross pathology receives ample consideration, a feature which is most essential for good practice of surgery. Illustrations are very abundant and most excellent.

The Medical Secretary†

THIS small volume is presented as a guide for doctors' secretaries and office assistants who have not had special training in this field. The advice given ranges all the way from personal appearance to the proper method of writing manuscripts for publication, and proof correction. The advice given is good and if the medical secretary were to conform to all specifications the doctor's office would run most smoothly and would be spotless. One might feel that a lot of the advice given is already obvious but when one enters some doctors' offices, one realizes that there should be a distinct need for a volume such as this that can be read and assimilated by a really ambitious secretary.

The trouble is that no matter what the qualifications of a doctor's secretary, usually his office reflects his own personality. However, it is entirely possible that a good secretary with a pride in her work and a loyalty to her employer might with the help of this small volume do wonders for a doctor who has failed to realize that the appearance and running of his office really are important from the point of view of the patient.

A third section of the book devoted to medical terminology is really a glossary of the more common medical terms. However, it would be well to emphasize that no medical secretary can get along well without a medical dictionary.

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*Surgical Pathology. By William Boyd, M.D., M.R.C.P. Ed., F.R.C.P. Lond., Dipl. Psych. F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Third Edition. Thoroughly Revised with 477 Illustrations and 13 Colored Plates, cloth, pages 866. W. B. Saunders Company, Philadelphia, and London, 1933.

†The Medical Secretary. By Minnie Genevieve Morse. Member Board of Registration, Association of Record Librarians of North America. Author of "Case Records in Small Hospitals." Cloth, pages 162. The Macmillan Company, New York, 1933.

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EDITORIAL

AIR BORNE MOLDS

THE allergist whose interest in air borne pollens takes him to the botanist for aid in the identification of weeds often finds to his surprise that the botanist knows very little of the taxonomy of the ordinary weeds and grasses. His interest both in the classroom and the field has been primarily in the brightly colored flowers and the trees. In the same way the bacteriologist has been only too well acquainted for many years with the air borne molds which are so prone to contaminate culture media, and which, indeed, he speaks of, as the weeds of the bacteriological laboratory.

When it was discovered that molds and yeasts do actually produce morbid lesions not only in the skin but in the internal organs some attention was necessarily given to this form of microorganism, but the pathologist has probably contributed as much to our knowledge in this field as has the bacteriologist. Now, since it has been found that air borne molds may be responsible for disease particularly in the allergic patient, the medical mycologist finds it desirable to acquaint himself more intimately with the weeds of the laboratory. One who has made no special studies in this field might feel that there would be considerable difficulty in finding altogether satisfactory source books for reference. As a matter of fact some very excellent reference volumes are avail-

able which deal with just those phases of the mycology of air borne molds which will be of special interest to the bacteriologist and the clinician. While there are others, some of them more detailed, two most satisfactory books are *Bacteriology* by Buchanan and Henrici's *Molds, Yeasts, and Actinomycetes.* One will rarely have occasion for more detailed information than is contained in these volumes but in such an event Stevens' *Plant Disease Fungi* provides a very complete classification, while *The Aspergilli* by Thom and Church and *The Penicillia* by Thom provides the last word in the classification of these two great groups of molds.

Mold spores are quite ubiquitous as will be vouched for by any bacteriologist, housewife or sailwright. The spore count of molds in the air varies from a matter of hundreds in the outside air to tens of thousands or even hundreds of thousands per cubic yard of air in buildings. They exist in the ground to a depth varying around four feet but are most numerous near the surface. In the earth they serve a useful purpose chiefly by breaking down cellulose into its simpler derivatives and by fixing nitrogen thereby preventing it from leaching out. Sometimes they form an almost symbiotic relationship with the roots of trees, preparing the nutritive substances in the immediate vicinity for absorption by the roots. It is said that the orchid requires its symbiotic mold for existence.

While air borne molds and yeasts are deleterious in certain industries, causing spoilage, in others they are employed to great advantage. In the Orient a mold is used to convert rice into sugar for the manufacture of alcoholic beverages. There, and in this country, *Aspergillus oryzae,* the aspergillus of rice is employed for the manufacture of a diastatic ferment, marketed as Takadiastase. The citromyces and other molds have been used for the manufacture of citric acid. The dark brown sauce used in Chinese restaurants is a product of the fermentation of *Aspergillus oryzae.* Many cheeses are ripened with molds, the most important of which are Camembert and Roquefort, which are ripened through the activity of the proteolytic ferment of a penicillium. Yeasts are employed in the fermentation of wines, beers, and in the making of bread.

Many of the air borne molds have been found to be responsible for allergic coryza and asthma, and these fortunately include most of the common ones such as the mucors, the aspergilli, the penicillia, alternaria. It is of course a logical observation that the commoner air borne molds should be responsible for this type of reaction.

The clinical bacteriologist will as time goes on in all probability develop an increasing interest not only in the pathogenic molds but in the nonpathogens mentioned above.

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—*W. T. V.*